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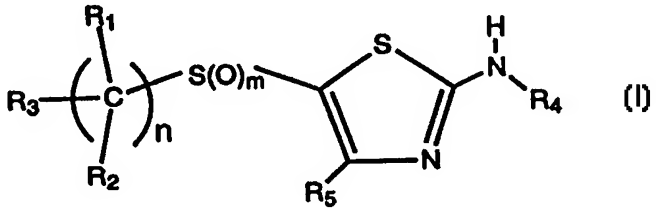
(54) Title: AMINOTHIAZOLE INHIBITORS OF CYCLIN DEPENDENT KINASES



(I)

(57) Abstract

Compounds of formula (I) and pharmaceutically acceptable salts thereof. As used in formula (I), and throughout the specification, the symbols have the following meanings: R_1 and R_2 are independently hydrogen, fluorine or alkyl; R_3 is aryl or heteroaryl. The compounds of formula (I) are protein kinase inhibitors and are useful in the treatment and prevention of proliferative diseases, for example cancer, inflammation and arthritis.

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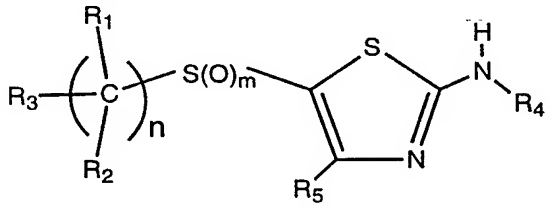
AMINOTHIAZOLE INHIBITORS OF CYCLIN DEPENDENT KINASES

Brief Description of the Invention

The present invention is directed to compounds of the formula



(I)

and pharmaceutically acceptable salts thereof. As used in formula I, and throughout the specification, the symbols have the following meanings:

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is aryl or heteroaryl

R_4 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

SO_2-alkyl, SO_2-cycloalkyl, SO_2-aryl, SO_2-alkyl-cycloalkyl, SO_2-alkyl-aryl, SO_2-heteroaryl, SO_2-alkyl-heteroaryl, SO_2-heterocycloalkyl, SO_2-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl,

C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl;

or

$C(NNO_2)$NH-alkyl, $C(NNO_2)$NH-cycloalkyl, $C(NNO_2)$NH-aryl, $C(NNO_2)$NH-alkyl-cycloalkyl, $C(NNO_2)$NH-alkyl-aryl, $C(NNO_2)$NH-heteroaryl, $C(NNO_2)$NH-alkyl-heteroaryl, $C(NNO_2)$NH-heterocyloalkyl, $C(NNO_2)$NH-alkyl-heterocycloalkyl;

or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

$C(NOR_6)$NH-alkyl, $C(NOR_6)$NH-cycloalkyl, $C(NOR_6)$NH-aryl, $C(NOR_6)$NH-alkyl-cycloalkyl, $C(NOR_6)$NH-alkyl-aryl, $C(NOR_6)$NH-heteroaryl, $C(NOR_6)$NH-alkyl-heteroaryl, $C(NOR_6)$NH-heterocylcoalkyl, $C(NOR_6)$NH-alkyl-heterocycloalkyl;

R_5 is hydrogen or alkyl;

R_6 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

The compounds of formula I are protein kinase inhibitors and are useful in the treatment and prevention of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, viral diseases and fungal diseases.

Description of the Invention

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

It should be noted that any heteroatom with unsatisfied valances is assumed to have the hydrogen atom to satisfy the valances.

Carboxylate anion refers to a negatively charged group $-COO^-$.

The term "alkyl" or "alk" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 12 carbon atoms unless otherwise defined. An alkyl group is an optionally substituted straight, branched or cyclic saturated hydrocarbon group. When substituted, alkyl groups may be substituted with up to four substituent groups, R as defined, at any available point of attachment. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group". Exemplary unsubstituted such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. Exemplary substituents may include but are not limited to one or more of the following groups: halo (such as F, Cl, Br, I), haloalkyl (such as CCl_3 or CF_3), alkoxy, alkylthio, hydroxy, carboxy (-COOH), alkyloxycarbonyl (-C(O)R), alkylcarbonyloxy (-OCOR), amino ($-NH_2$), carbamoyl (-NHCOOR- or -OCONHR-), urea (-NHCONHR-) or thiol (-SH). Alkyl groups as defined may also comprise one or more carbon to carbon double bonds or one or more carbon to carbon triple bonds.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon double bond.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond.

Cycloalkyl is a specie of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings. Exemplary unsubstituted such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, etc. Exemplary substituents include one or more of the following groups: halogen, alkyl, alkoxy, alkyl hydroxy, amino, nitro, cyano, thiol and/or alkylthio.

The terms "alkoxy" or "alkylthio", as used herein, denote an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively.

The term "alkyloxycarbonyl", as used herein, denotes an alkoxy group bonded through a carbonyl group. An alkoxycarbonyl radical is represented by the formula: -C(O)OR, where the R group is a straight or branched C_{1-6} alkyl group.

The term "alkylcarbonyl" refers to an alkyl group bonded through a carbonyl group.

The term "alkylcarbonyloxy", as used herein, denotes an alkylcarbonyl group which is bonded through an oxygen linkage.

The term "arylalkyl", as used herein, denotes an aromatic ring bonded to an alkyl group as described above.

The term "aryl" refers to monocyclic or bicyclic aromatic rings, e.g. phenyl, substituted phenyl and the like, as well as groups which are fused, e.g., napthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Aryl groups may optionally be substituted with one or more groups including, but not limited to halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, nitro, trifluoromethyl, amino, cycloalkyl, cyano, alkyl $S(O)_m$ (m=O, 1, 2), or thiol.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S, or N, in which a carbon or nitrogen atom is the point of attachment, and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Exemplary heteroaryl groups include the following: thienyl, furyl, pyrrolyl, pyridinyl, imidazolyl, pyrrolidinyl, piperidinyl, thiazolyl, oxazolyl, triazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyrazinyl, pyridazinyl, pyrimidinal, triazinylazepinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzoxadiazolyl, benzofurazanyl and tetrahydropyranyl. Exemplary substituents include one or more of the following: halogen, alkyl, alkoxy, hydroxy, carboxy, carbamoyl, alkyloxycarbonyl, trifluoromethyl, cycloalkyl, nitro, cyano, amino, alkyl$S(O)_m$ (m=0, 1, 2), or thiol.

The term "heteroarylium" refers to heteroaryl groups bearing a quaternary nitrogen atom and thus a positive charge.

The term "heterocycloalkyl" refers to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms.

The term "quaternary nitrogen" refers to a tetravalent positively charged nitrogen atom including, e.g. the positively charged nitrogen in a tetraalkylammonium group (e.g. tetramethylammonium, N-methylpyridinium), the positively charged nitrogen in protonated ammonium species (e.g. trimethylhydroammonium, N-hydropyridinium), the positively charged nitrogen in amine N-oxides (e.g. N-methyl-morpholine-N-oxide, pyridine -N-oxide), and the positively charged nitrogen in an N-amino-ammonium group (e.g. N-aminopyridinium).

The term "heteroatom" means O, S or N, selected on an independent basis.

The term "halogen" or "halo" refers to chlorine, bromine, fluorine or iodine.

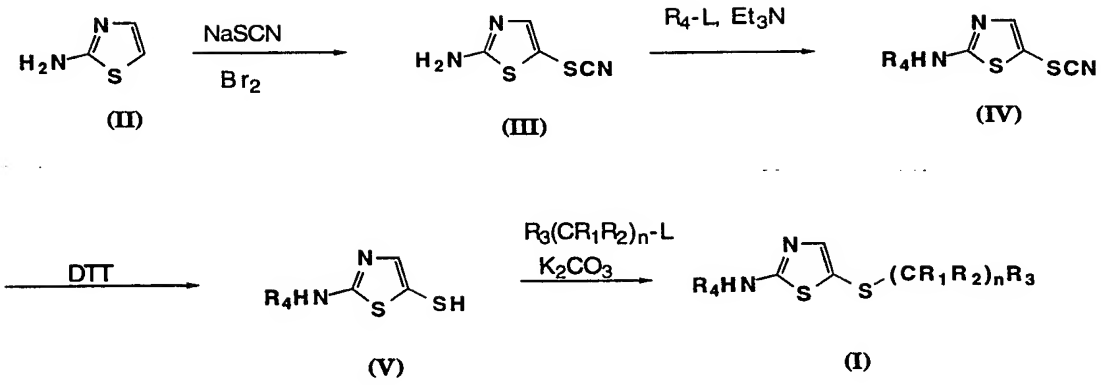
When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

Suitable examples of salts of the compounds according to the invention with inorganic or organic acids are hydrochloride, hydrobromide, sulfate, phosphate. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The definition of the compounds according to the invention embraces all possible stereoisomers and their mixtures. It very particularly embraces the racemic forms and the isolated optical isomers having the specified activity. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

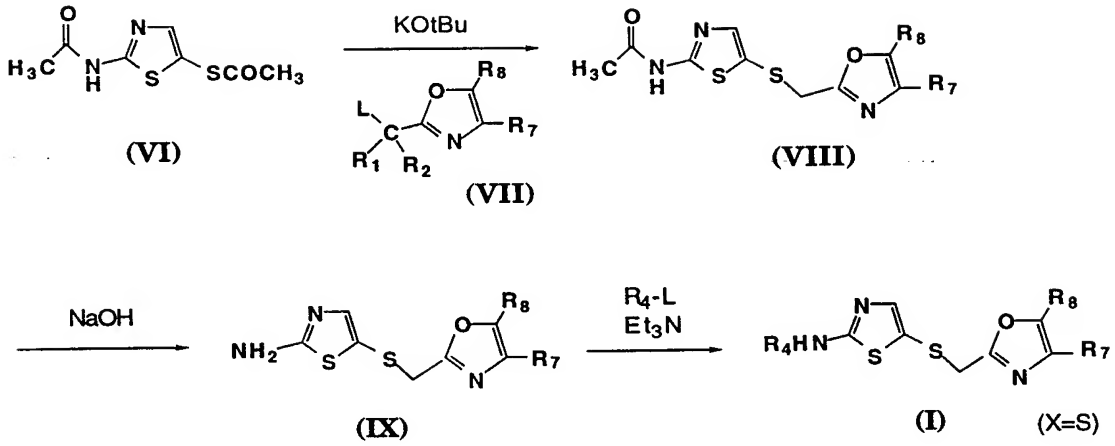
It should be understood that solvates (e.g., hydrates) of the compounds of formula I are also within the scope of the present invention. Methods of solvation are generally known in the art. Accordingly, the compounds of the instant invention may be in the free or hydrate form, and may be obtained by methods exemplified by the following schemes.

Scheme 1



As illustrated in Scheme 1, compounds of formula I where X is S are prepared by reacting 2-aminothiazole (II) with bromine in the presence of sodium or potassium thiocyanate to obtain a thiocyanated aminothiazole, specifically 5-thiocyanatoaminothiazole (III). Compound III is then reacted with R_4-L, where L is a leaving group such as a halogen, in the presence of a base such as triethylamine to provide a 5-thiocyanatothiazole intermediate (IV), where R_4 is as defined in the specification. The intermediate (IV) is then reduced to a thiol (V) using reducing agents such as dithiothreitol (DTT), sodium borohydride, zinc or other known reducing agents. Compound (V) is then reacted with alkyl, aryl or heteroaryl halides, such as R_3 $(CR_1R_2)_n$-L, where L is a leaving group such as a halogen, in the presence of a base such as potassium carbonate to obtain compounds of formula I. The steps of reducing the thiocyanothiazole intermediate (IV) to the thiol (V), and the reaction of the reduced thiol (V) to provide compounds of formula I where X is S, may be carried out sequentially without purification.

Scheme 2



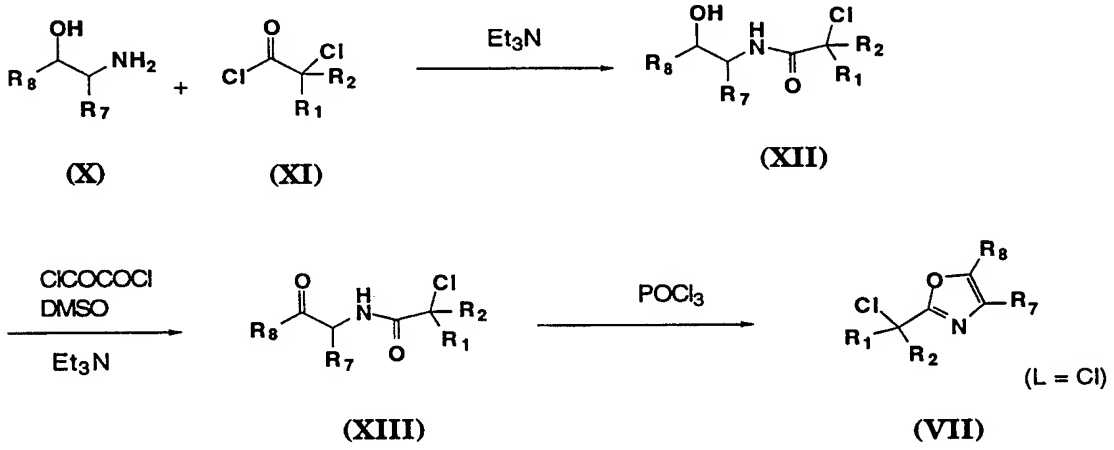
In Scheme 2, 5-thioacetyl-2-acetylaminothiazole of structure VI is reacted with an alkoxide such as potassium t-butoxide in alcohol or THF solvent and the resulting thiol is reacted *in situ* with a group of formula $R_3(CR_1R_2)_n$-L (where L is a leaving group, such as a halogen) such as 2-halomethyloxazole (VII) to provide a compound such as formula VIII, wherein R_1 and R_2 are hydrogen, and R_6 is acetyl. The 2-halomethyloxazole compounds of formula VII may be prepared using several synthetic routes known in the art. *Chem. Pharm. Bull.* 30, 1865 (1982); *Bull. Chem. Soc. Japan* (52, 3597 (1979); *JCS Chem. Comm.* 322 (1981); *Comprehensive Heterocyclic Chemistry*, vol. 6, 177, edited by A. Katritzky and C.W. Rees, Pergamon Press (1984).

Compounds of formula VIII (a compound of formula I where R_4 is acetyl and X is sulfur) can be hydrolyzed in the presence of a base such as sodium hydroxide to provide a compound of formula IX. A compound of formula IX may then be reacted with R_4-L, in the presence of a base such as triethylamine, where L is a leaving group such as a halogen, to give compounds of formula I where X is sulfur. In this manner, compounds of formula IX, which is a compound of formula I where R_4 is hydrogen, can be treated with agents such as isothiocyanates, halides, acyl halides, chloroformates, isocyanates or sulfonyl chlorides to provide thioureas, amines, amides, carbamates, ureas or sulfonamides. The

procedures in Scheme 2 specifically illustrate a methyloxazole group, but are general for all $R_3(CR_1R_2)_n$- groups specified by formula I.

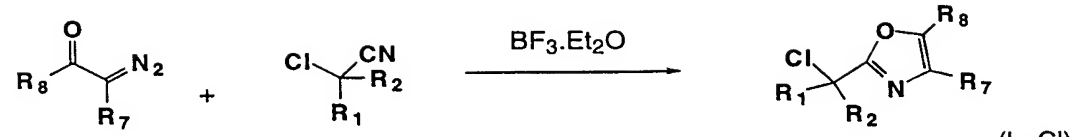
Alternatively, compounds of formula VII, where L is bromine, may be prepared by halogenation of 2-methyloxazole using N-bromosuccinimide in the presence of dibenzoylperoxide.

Scheme 3



Scheme 3 illustrates an alternative method of preparing compound VII, which is a compound of formula $R_3(CR_1R_2)_n$-L where L is chlorine and n is the integer 1. In this scheme, compound VII is prepared by the reaction of a compound of formula X and formula XI in the presence of a base such as triethylamine to provide compounds of formula XII. Compound XII may be oxidized by an oxidant such as oxalylchloride/DMSO in the presence of a base such as triethylamine to provide a compound of formula XIII which may be cyclized by an agent such as phosphorous oxychloride to provide compounds of formula VII, wherein L is chlorine. Alternatively, compounds of formula XIII may be prepared by reaction of the amino ketone correponding to X with an acid chloride such as XI.

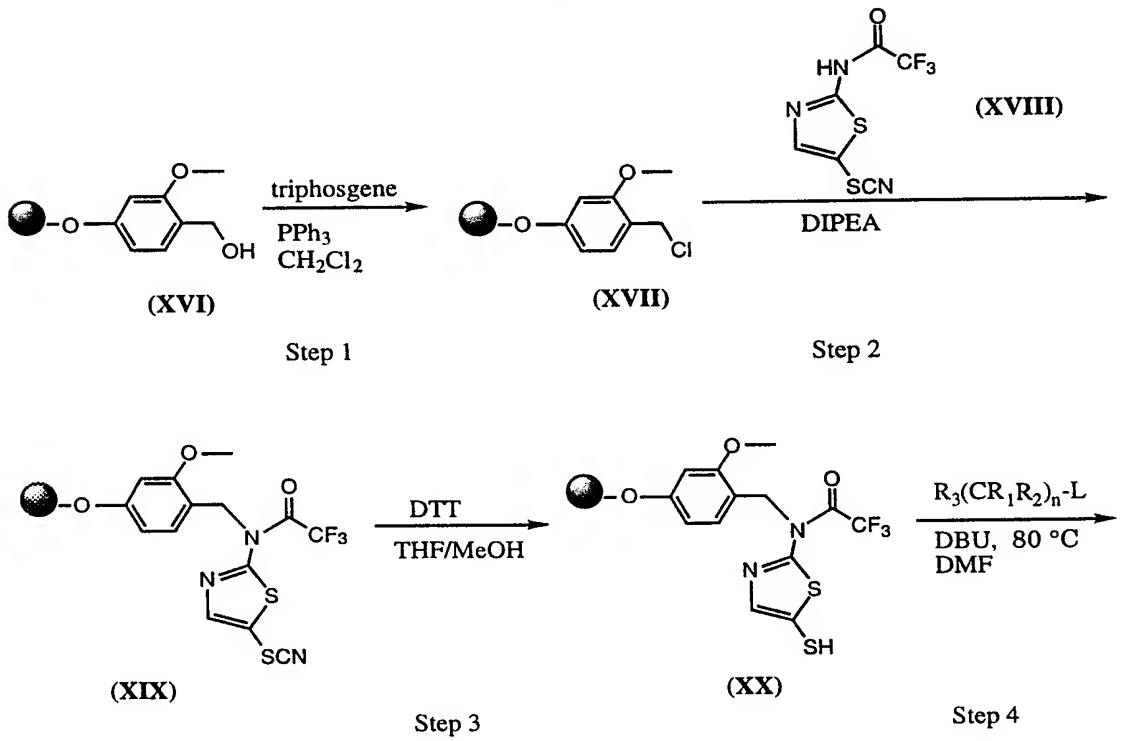
Scheme 4



(XIV) **(XV)** **(VII)**

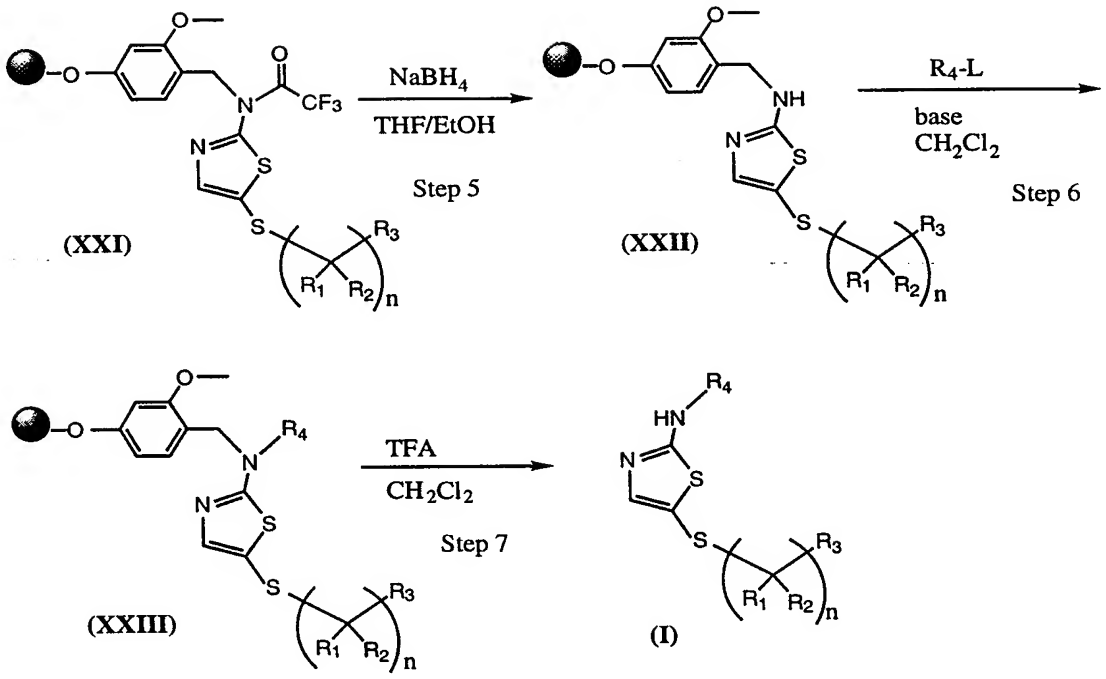
Compounds of formula VII, where L is chlorine, may also be prepared from the reaction of diazoketones as illustrated by formula XIV in Scheme 4 with chloronitriles, such as indicated by formula XV, in the presence of BF_3 etherate to provide compounds of formula VII, wherein L is chlorine.

Scheme 5



(XVI) **(XVII)** **(XVIII)** **(XIX)** **(XX)**

Step 1 Step 2 Step 3 Step 4



In Scheme 5, starting compound XVI denotes a resin-bound benzyl alcohol support used for solid phase synthesis which is prepared from a Merrifield resin denoted as ●, and 2-methoxy-4-hydroxybenzaldehyde, followed by reduction with reducing agents such as $NaBH_4$. In step 1, starting compound XVI is treated with triphosgene and triphenylphosphine (PPh_3) in dichloromethane to give the chlorobenzyl resin of formula XVII. In step 2, a thiocyanato trifluoroacetamide (XVIII) is alkylated with the resin-bound benzyl chloride (XVII) in the presence of diisopropylethylamine (DIPEA) to form a resin-bound thiocyanate (XIX). The thiocyanato trifluoroacetamide compound of formula XVII is prepared by reacting 5-thiocyanatoaminothiazole of formula III (Scheme I) with trifluoroacetic anhydride using a base such as 2,6-lutidine.

The resin-bound thiocyanate (XIX) is then reduced to a resin-bound thiol (XX) in step 3 with reducing agent such as dithiothreitol (DTT) in tetrahydrofuran (THF) and methanol. The resulting resin-bound thiol (XX) is reacted with $R_3(CR_1R_2)_n$-L, where L is a leaving group, in the presence of a base such as 1,8-diazabicyclo[5,4,0]undec-7-

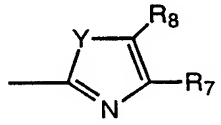
ene (DBU) at 80 °C in dimethylformamide (DMF) to form compounds of formula XXI (step 4). Deprotection of the trifluoroacetyl group of compound XXI is performed in step 5 using sodium borohydride to provide a compound of formula XXII. In step 6, the deprotected compound XXII is reacted with R_6X, where X is a leaving group, in the presence of a base such as diisopropylethylamine to provide compounds of formula XXIII. The product is then cleaved from the solid phase resin in step 7 with trifluoroacetic acid (TFA) to give compounds of formula I where X is sulfur. Compounds of formula I where X is $S(O)_m$ and m is 1 or 2 may be prepared from compounds of formula I where m is 0 by oxidation with an oxidant such as sodium periodate, meta-chloroperbenzoic acid, or oxone.

The starting compounds of Schemes 1-5 are commercially available or may be prepared by methods known to one of ordinary skill in the art.

All compounds of formula I may be prepared by modification of the procedures described herein.

The preferred compounds of formula I are those where:

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is oxygen, sulfure or NR_9;

R_4 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

SO_2-alkyl, SO_2-cycloalkyl, SO_2-aryl, SO_2-alkyl-cycloalkyl, SO_2-alkyl-aryl, SO_2-heteroaryl, SO_2-alkyl-heteroaryl, SO_2-heterocycloalkyl, SO_2-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

$C(NNO_2)NH$-alkyl, $C(NNO_2)NH$-cycloalkyl, $C(NNO_2)NH$-aryl, $C(NNO_2)NH$-alkyl-cycloalkyl, $C(NNO_2)NH$-alkyl-aryl, $C(NNO_2)NH$-heteroaryl, $C(NNO_2)NH$-alkyl-heteroaryl, $C(NNO_2)NH$-heterocyloalkyl, $C(NNO_2)NH$-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

$C(NOR_6)NH$-alkyl, $C(NOR_6)NH$-cycloalkyl, $C(NOR_6)NH$-aryl, $C(NOR_6)NH$-alkyl-cycloalkyl, $C(NOR_6)NH$-alkyl-aryl, $C(NOR_6)NH$-heteroaryl, $C(NOR_6)NH$-alkyl-heteroaryl, $C(NOR_6)NH$-heterocylcoalkyl, $C(NOR_6)NH$-alkyl-heterocycloalkyl;

R_5 is hydrogen; and

R_6 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R_7 and R_8 are independently hydrogen, alkyl, cycloalkyl, aryl, alkylcycloalkyl, alkylaryl, heteroaryl, alkylheteroaryl, heterocycloalkyl, alkylheterocycloalkyl or halogen;

R_9 is H or alkyl;

m is the integer 0; and

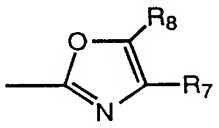
n is the integer 1.

The most preferred compounds of formula I are those where:

R_1 is hydrogen;

R_2 is hydrogen, fluorine or alkyl;

R_3 is a substituted oxazole having the configuration:



;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-cycloalkyl, CO-alkyl-heteroaryl, CO-alkyl-heteroalkyl, CO-alkyl-heterocycloalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_7 is hydrogen;

R_8 is an alkyl group, such as tert-butyl;

m is the integer 0; and

n is the integer 1.

The compounds according to the invention have pharmacological properties; in particular, the compounds of formula I are inhibitors of protein kinases such as the cyclin dependent kinases (cdks), for example, cdc2 (cdk1), cdk2, and cdk4. The novel compounds of formula I are expected to be useful in the therapy of proliferative diseases such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurodegenerative disorders and cardiovascular disease.

More specifically, the compounds of formula I are useful in the treatment of a variety of cancers, including (but not limited to) the following:

-carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma;

-hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burkett's lymphoma;

-hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

-tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

- tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

-other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of cdks in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of formula I may also be useful in the treatment of Alzheimer's disease, as suggested by the recent finding that cdk5 is

involved in the phosphorylation of tau protein (*J. Biochem*, 117, 741-749 (1995)).

Compounds of formula I may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of formula I, as modulators of apoptosis, will be useful in the treatment of cancer (including but not limited to those types mentioned hereinabove), viral infections (including but not limited to herpevirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of formula I, as inhibitors of the cdks, can modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of formula I may also be useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of pre-malignant cells that have already suffered an insult or inhibiting tumor relapse.

Compounds of formula I may also be useful in inhibiting tumor angiogenesis and metastasis.

Compounds of formula I may also act as inhibitors of other protein kinases, e.g., protein kinase C, her2, raf l, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, wee1 kinase, Src, Abl and thus be effective in the treatment of diseases associated with other protein kinases.

The compounds of this invention may also be useful in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methoxtrexate.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent or treatment within its approved dosage range. For example, the cdc2 inhibitor olomucine has been found to act synergistically with known cytotoxic agents in inducing apoptosis (*J. Cell Sci.*, 108, 2897 (1995)). Compounds of formula I may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of formula I may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the sequence of administration with anticancer agents. *Cancer Research*, 57, 3375 (1997).

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which follow have been carried

out with the compounds according to the invention and their salts. The compounds of examples 1 to 8 exhibited cdc2/cyclin B1 kinase activity with IC_{50} values less than 50 μM. The compounds of examples 1 to 8 exhibited cdk2/cyclin E kinase activity with IC_{50} values less than 50 μM. The compounds of examples 1 to 8 exhibited cdk4/cyclin D1 kinase activity with IC_{50} values less than 50 μM.

cdc2/cyclin B1 Kinase Assay

cdc2/cyclin B1 kinase activity was determined by monitoring the incorporation of ^{32}P into histone H1. The reaction consisted of 50 ng baculovirus expressed GST-cdc2, 75 ng baculovirus expressed GST-cyclin B1, 1 μg histone HI (Boehringer Mannheim), 0.2 mCi of ^{32}P g-ATP and 25 mM ATP in kinase buffer (50 mM Tris, pH 8.0, 10 mM $MgCl_2$, 1 mM EGTA, 0.5 mM DTT). The reaction was incubated at 30°C for 30 minutes and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15% and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and the filters were counted on a Packard TopCount 96-well liquid scintillation counter (Marshak, D.R., Vanderberg, M.T., Bae, Y.S., Yu, I.J., *J. of Cellular Biochemistry*, 45, 391-400 (1991), incorporated by reference herein).

cdk2/cyclin E Kinase Assay

cdk2/cyclin E kinase activity was determined by monitoring the incorporation of ^{32}P into the retinoblastoma protein. The reaction consisted of 2.5 ng baculovirus expressed GST-cdk2/cyclin E, 500 ng bacterially produced GST-retinoblastoma protein (aa 776-928), 0.2 mCi ^{32}P g-ATP and 25 mM ATP in kinase buffer (50 mM Hepes, pH 8.0, 10 mM $MgCl_2$, 5 mM EGTA, 2 mM DTT). The reaction was incubated at 30°C for 30 minutes and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15% and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and

the filters were counted on a Packard TopCount 96-well liquid scintillation counter.

cdk 4/cyclin D1 Kinase Activity

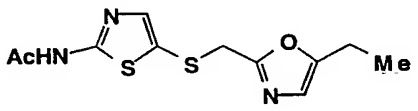
cdk4/cyclin D1 kinase activity was determined by monitoring the incorporation of ^{32}P in to the retinoblastoma protein. The reaction consisted of 165 ng baculovirus expressed as GST-cdk4, 282 ng bacterially expressed as S-tag cyclin D1, 500 ng bacterially produced GST-retinoblastoma protein (aa 776-928), 0.2μCi ^{32}P γ-ATP and 25 μM ATP in kinase buffer (50 mM Hepes, pH 8.0, 10 mM $MgCl_2$, 5 mM EGTA, 2 mM DTT). The reaction was incubated at 30°C for 1 hour and then stopped by the addition of cold trichloroacetic acid (TCA) to a final concentration of 15% and incubated on ice for 20 minutes. The reaction was harvested onto GF/C unifilter plates (Packard) using a Packard Filtermate Universal harvester, and the filters were counted on a Packard TopCount 96-well liquid scintillation counter (Coleman, K.G., Wautlet, B.S., Morissey, D, Mulheron, J.G., Sedman, S., Brinkley, P., Price, S., Wedster, K.R. (1997). Identification of CDK4 Sequences involved in cyclin D, and p16 binding. *J. Biol. Chem.* 272,30:18869-18874, incorporated by reference herein).

Further subject matter of the invention also includes pharmaceuticals for use as described above including controlling cancer, inflammation and arthritis, which contain at least one compound of the formula I as defined above or at least one of its pharmacologically acceptable acid addition salts, and the use of a compound of the formula I as defined above for the preparation of a pharmaceutical having activity against proliferative diseases as described previously including against cancer, inflammation and/or arthritis.

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto.

Example 1

N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide



A. Preparation of 1-benzyloxycarbonylamino-2-butanol

A mixture of 1-amino-2-butanol (5.5 g, 61.8 mmol), benzyl chloroformate (11.5 g, 67.6 mmol) and sodium carbonate (7.16 g, 67.7 mmol) in water (50 mL) was stirred at 0 °C for 3 h. Water (50 mL) was added to the reaction mixture and the product was extracted with methylene chloride (3x20 mL). The methylene chloride extract was dried over Na_2SO_4 and concentrated. The residue was passed through a short column (SiO_2, hexanes : ethyl acetate /10 : 1; then ethyl acetate) to afford 1-benzyloxycarbonylamino-2-butanol (13.9 g, 100%) as a liquid.

^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.45 (s, 1 H), 5.06 (s, 2 H), 3.57 (s, 1 H), 3.31 (m, 1 H), 3.04 (m, 1 H), 2.91 (m, 1 H), 1.43 (m, 2 H), 0.91 (t, J = 7.6 Hz, 3 H).

B. Preparation of 1-benzyloxycarbonylamino-2-butanone

To methylene chloride (60 mL) at -78 °C under argon was added oxalyl chloride (37 mL of 2 M solution in methylene chloride, 74 mmol), followed by DMSO (7.8 g, 100 mmol). The mixture was stirred at -78 °C for 20 min. and to this mixture was added a solution of 1-benzyloxycarbonylamino-2-butanol (13.9 g, 61.8 mmol) in methylene chloride (40 mL). The mixture was stirred at -78 °C for 1 h and triethylamine (21 mL) was added to the mixture. It was warmed to room temperature (rt) and washed successively with 1 N hydrochloric acid and aqueous sodium bicarbonate solution. The methylene chloride solution was dried over $MgSO_4$ and concentrated to afford 1-benzyloxycarbonylamino-2-butanone (11.2 g, 82%) as a solid, which was enough pure for the next reaction.

^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5 H), 5.50 (s, 1 H), 5.06 (s, 2 H), 4.07 (s, 2 H), 2.43 (q, J = 7.6 Hz, 2 H), 1.06 (t, J = 7.6 Hz, 3 H).

C. Preparation of 1-amino-2-butanone

A solution of 1-benzyloxycarbonylamino-2-butanone (9.30 mg, 42 mmol) in ethanol (50 mL) and 1 N hydrochloric acid (46 mL) was stirred under hydrogen atmosphere in the presence of Pd/C (1.5 g, 10%) at rt for 4 h. The mixture was filtered through a celite bed and the filtrate solution was concentrated. The residue was triturated with ethyl ether to afford 1-amino-2-butanone (5.3 g, 102%) as a hydrochloride salt.

^{1}H NMR (CD_3OD) δ 3.97 (s, 2 H), 2.60 (q, J = 7.6 Hz, 2 H), 1.08 (t, J = 7.6 Hz, 3 H).

D. Preparation of 2-amino-5-thiocyanatothiazole

2-Aminothiazole (41g, 410 mM) and sodium thiocyanate (60 g, 740 mM, dried in a vacuum oven at 130 °C overnight) was dissolved in 450 mL of anhydrous methanol and the solution was cooled in a cold water bath. Here was added bromine (23 mL, 445 mM) dropwise with good stirring. After the addition it was stirred for 4 h at rt. To the mixture 500 mL of water was added and it was stirred for 5 minutes, filtered through a celite bed and washed the bed with water. The pH of the filtrate solution was about 1. Most of the methanol was removed under the reduced pressure and pH of the solution was adjusted to about 7 by adding aq. sodium carbonate slowly with stirring. The precipitated solid was filtered and washed with water to obtain 37 g (57%) of the dark brown colored desired product after drying, mp 140-143 °C.

^{1}H NMR (CD_3OD) δ 7.33 (s, 1H); MS (CI/NH_3) m/e 179 $(M+Na)^+$, 158$(M+H)^+$.

E. Preparation of of 2-acetylamino-5-thiocyanatothiazole

To a mixture of 2-amino-5-thiocyanatothiazole (15.7 g, 0.1 mol) and pyridine (12 g, 0.15 mol) in methylene chloride (100 mL) was added acetic

anhydride (1.2 g, 0.12 mol) at rt. The mixture was stirred at rt for 6 h. The mixture was concentrated to dryness and to the residue MeOH (50 mL) was added. The precipitates were collected and washed with water. The solid was dried and recrystallized from MeOH to afford 2-acetylamino-5-thiocyanatothiazole (15.2 g, 76%) as a solid, mp 212 °C.

^{1}H NMR (CD_3OD) δ 7.79 (s, 1H), 2.23 (s, 3 H).

F. Preparation of [[2-(acetylamino)-5-thiazolyl]thio]acetic acid 1,1-dimethylethyl ester

To a mixture of 2-acetamino-5-thiocyanatothiazole (5.97 g, 30 mmol) in MeOH (360 mL) under argon was added dithiothreitol (9.26 g, 60 mmol) at rt. The mixture was stirred at rt for 2 h and it was concentrated to afford a reduced solid product. This solid product was dissolved in DMF (30 mL) and to this solution were added tert-butyl bromoacetate (5.85 g, 30 mmol) and potassium carbonate (5.0 g, 36 mmol). The mixture was stirred at rt for 2 h and water (200 mL) was added to the mixture. The precipitates were collected, washed with water and dried. The solid was dissolved in methylene chloride (100 mL) and MeOH (10 mL) and filtered through a silica gel pad. The filtrate solution was concentrated to afford the desired product (7.5 g, 87%) as a solid, mp 162-163 °C.

^{1}H NMR ($CDCl_3$) δ 12.2 (s, 1 H), 7.48 (s, 1 H), 3.37 (s, 2 H), 2.32 (s, 3 H), 1.45 (s, 9 H); MS m/e 289 $(M+H)^+$, 287 $(M-H)^-$.

HPLC (Column: YMC S3 ODS 4.6x150mm; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10% MeOH-90% water-0.2% H_3PO_4; Solvent B: 90% MeOH-10% Water-0.2% H_3PO_4; UV: 220 nm): retention time 6.44 min.

G. Preparation of [[2-(acetylamino)-5-thiazolyl]thio]acetic acid

A solution of [[2-(acetylamino)-5-thiazolyl]thio]acetic acid 1,1-dimethylethyl ester (4.32 g, 15 mmol) in methylene chloride (30 mL) and trifluoroacetic acid (20 mL) was stirred at rt overnight and concentrated *in*

vacuo. To the residue was added ethyl ether (50 mL). The precipitated solid was collected, washed with ethyl ether and dried to afford the desired product (3.38 g, 97%) as a solid, mp 210 °C.

^{1}H NMR (CD_3OD) δ 7.48 (s, 1 H), 3.47 (s, 2 H), 2.20 (s, 3 H) ppm; MS m/e 231$(M-H)^-$; HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10% MeOH-90% water-0.2%H_3PO_4; Solvent B: 90% MeOH-10% Water-0.2% H_3PO_4; UV: 254 nm): retention time 4.32 min.

H. Preparation of [[2-(acetylamino)-5-thiazolyl]thio]-N-(2-oxobutyl)acetamide

A mixture of [[2-(acetylamino)-5-thiazolyl]thio]acetic acid (9.0 g, 38.8 mmol), HOBT (5.94 g, 38.8 mmol) and ethyldimethylaminopropylcarbodiimide hydrochloride salt (11.16 g, 58.2 mmol) in DMF (50 mL) was stirred at 0 °C for 0.5 h. To this mixture was added 1-amino-2-butanone hydrochloride (5.27 g, 42.7 mmol) followed by triethylamine (15 mL, 107.5 mmol). The mixture was stirred at 0 °C for 0.5 h and at rt for 1 h. Water (200 mL) was added to the mixture and the product was extracted with methylene chloride containing 10% MeOH (5x100 mL). The methylene chloride extract was dried over Na_2SO_4 and concentrated. The residue was triturated with water and the precipitated solid product was collected by filtration. It was dried to obtain the desired product (10.5 g, 90%), mp 195-196 °C.

^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1 H), 4.14 (s, 2 H), 3.46 (s, 2 H), 2.50 (q, J = 7.6 Hz, 2 H), 2.25 (s, 3 H), 1.12 (t, J = 7.6 Hz, 3 H); MS m/e 302 $(M+H)^+$.
HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2%H_3PO_4; Solvent B: 90%MeOH-10%Water-0.2%H_3PO_4; UV: 254 nm): retention time 4.36 min.

I. Preparation of N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide

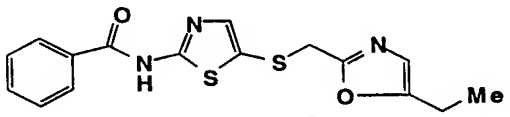
To a solution of [[2-(acetylamino)-5-thiazolyl]thio]-N-(2-oxobutyl)acetamide (10.5 g, 34.8 mmol) in acetic anhydride (100 mL) was added conc. sulfuric acid (10 mL). The mixture was stirred at 55-60 °C for 2 h and sodium acetate (15 g, 0.18 mol) was added to the mixture. The mixture was concentrated *in vacuo*. To the residue was added cold water (100 mL). The precipitated solid was collected, washed with water and dried. It was purified by a flash column chromatography (SiO_2; methylene chloride : MeOH / 100 : 5) to afford N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide (4.2 g, 43%) as a solid, mp 147-148 °C.

^1H NMR ($CDCl_3$) δ 12.47 (s, 1 H), 7.29 (s, 1 H), 6.61 (s, 1 H), 3.91 (s, 2 H), 2.64 (q, J = 7.6 Hz, 2 H), 2.25 (s, 3 H), 1.21 (t, J = 7.6 Hz, 3 H) ppm; MS m/e 284 $(M+H)^+$;

HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2%H_3PO_4; Solvent B: 90%MeOH-10%Water-0.2%H_3PO_4; UV: 254 nm): retention time 6.50 min.

Example 2

N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzamide



A. Preparation of 2-amino-5-[[(5-ethyl-2-oxazolyl)methyl]thio]-thiazole

A solution of N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide (1.3 g, 4.6 mmol) in 1 N hydrochloric acid (15 mL) was stirred at 80-90 °C for 3 h. It was cooled to rt and the pH of the solution was adjusted to 7 with sodium carbonate. The product was extracted with

methylene chloride (3x10 mL). The combined extract was dried over Na_2SO_4 and concentrated. The residue was triturated with ethyl ether and the precipitated solid was collected to afford 2-amino-5-[[(5-ethyl-2-oxazolyl)methyl]thio]-thiazole (610 mg, 55%) as a solid, mp 119-120 °C.

^1H NMR ($CDCl_3$) δ 6.93 (s, 1 H), 6.61 (s, 1 H), 5.41 (s, 2 H), 3.82 (s, 3 H), 2.62 (q, J =7.6 Hz, 2 H), 1.18 (t, J = 7.6 Hz, 3 H); MS m/e 242 $(M+H)^+$;
HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2%H_3PO_4; Solvent B: 90%MeOH-10%Water-0.2%H_3PO_4; UV: 254 nm): retention time 3.96 min.

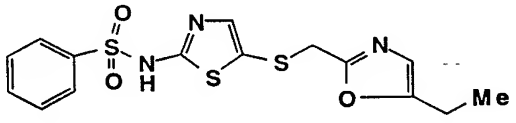
B. Preparation of N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzamide

A mixture of 2-amino-5-[[(5-ethyl-2-oxazolyl)methyl]thio]-thiazole (48.2 mg, 0.2 mmol), benzoyl chloride (24.4 mg, 0.21 mmol) and triethylamine (35 mg, 0.35 mmol) in methylene chloride (0.5 mL) was stirred at rt for 10 min. The organic solution was washed with water and concentrated. The residue was purified by a flash column (SiO_2; hexanes : ethyl acetate / 2 : 1) to afford N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzamide (41 mg, 59%) as a solid, mp 122-123 °C.

^1H NMR ($CDCl_3$) δ 12.65 (s, 1 H), 7.96 (m, 2 H), 7.61 (m,, 1 H), 7.49 (m, 2 H), 6.88 (s, 1 H), 6.56 (s, 1 H), 3.93 (s, 2 H), 2.61 (q, J = 7.6 Hz, 2 H), 1.20 (t, J = 7.6 Hz, 3 H); MS m/e 346 $(M+H)^+$;
HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2%H_3PO_4; Solvent B: 90%MeOH-10%Water-0.2%H_3PO_4; UV: 254 nm): retention time 7.94 min.

Example 3

N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzsulfoneamide



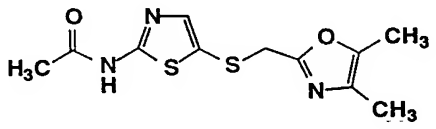
A mixture of 2-amino-5-[[(5-ethyl-2-oxazolyl)methyl]thio]-thiazole (24.1 mg, 0.1 mmol), benzenesulfonyl chloride (19.4 mg, 0.11 mmol) and triethylamine (22 mg, 0.21 mmol) in methylene chloride (0.3 mL) was stirred at rt for 10 h. The product of the reaction mixture was purified by preparative HPLC (column: YMC pack ODSA S3 20x100 mm; method: gradient from 0 % B to 100% B in 20 min and flow rate 20 mL/min; UV: 254 nm; solvent A: 10%MeOH-90%water-0.1%TFA; solvent B: 90%MeOH-10%water-0.1%TFA) to obtain N-[5-[[(5-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzsulfoneamide (2.5 mg) as a solid after drying via lyophilization.

^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1 H), (s, 2 H), 7.49 (m, 3 H), 6.89 (s, 1 H), 6.64 (s, 1 H), 4.01 (s, 2 H), 2.68 (q, J = 7.4 Hz, 2 H), 1.27 (t, J = 7.4 Hz, 3 H); MS m/e 382 $(M+H)^+$;

HPLC (column: Zorbax Rapid resolution C-18; flow rate: 2.5 mL/min; solvent system: 0-100% B in 8 min. Solvent A: 10%MeOH-90%water-0.2% H_3PO_4; Solvent B: 90%MeOH-10%Water-0.2% H_3PO_4; UV: 254 nm): retention time 6.84 min.

Example 4

N-[5-[[(4,5-dimethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide



A. Preparation of 2-(bromomethyl)-4,5-dimethyloxazole

A mixture of 2,4,5-trimethyloxazole (0.50 mL, 4.3 mmol), N-bromosuccinimide (0.77 g, 4.3 mmol) and benzoyl peroxide (0.21 g, 0.86 mmol) in carbon tetrachloride (4 mL) was heated at 76 °C under nitrogen atm.for 3 hrs. After cooling to rt, the solid was removed by filtration. The filtrate solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and concentrated. The residue was purified by flash column chromatography (SiO_2; hexanes:ethyl acetate / 4:1) to afford 2-(bromomethyl)-4,5-dimethyloxazole (64 mg) as an yellow oil.

^1H NMR ($CDCl_3$) δ 4.4 (s, 2 H), 2.25 (s, 3 H), 2.05 (s, 3 H).

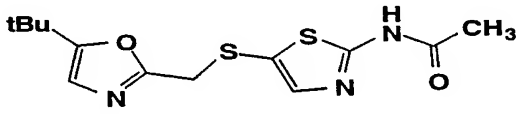
B. Preparation of N-[5-[[(4,5-dimethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide

N-[5-(Acetylthio)-2-thiazolyl]acetamide (0.050 g, 0.23 mmol) was dissolved in dry THF (10 ml) and here potassium*tert*-butoxide (1.0 M solution in THF, 0.25 ml, 0.25 mmol) was added to the mixture. The reaction mixture was stirred at rt for 15 min., and 2-(bromomethyl)-4,5-dimethyloxazole (0.064 g, 0.34 mmol) was added to this mixture. The reaction mixture was stirred at rt for 3 h and saturated aqueous $NaHCO_3$ solution (20 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers was concentrated. The residue was purified by flash column chromatography (SiO_2; methanol:dichloromethane /1:20) to afford N-[5-[[(4,5-dimethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide (15 mg, 23%) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ 11.78 (s, 1 H), 7.38 (s, 1 H), 3.90 (s, 2 H), 2.30 (s, 3H), 2.22 (s 3H), 2.05 (s, 3H); MS m/e 284 $(M+H)^+$;
HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 ml/min; solvent system: 0-100% B in 8 min. Solvent A: 10% CH_3OH/90% H_2O/0.2% H_3PO_4; Solvent B: 90% CH_3OH/10% H_2O/0.2% H_3PO_4; UV: 254 nm): retention time 5.87 min.

Example 5

N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide



A. Preparation of diazomethane

To a mixture of 15 ml of 40% aqueous KOH solution and 50 mL of diethyl ether at 0 °C was added 5 g (68 mmol) of N-methyl-N'-nitro-N-nitrosoguanidine in portions with stirring . The resulting mixture was stirred at 0 °C for 0.5 h. The organic phase was decanted into a dry flask and dried over solid KOH pellets to give 50 mL of diazomethane solution (ca 0.5 M, by titrating with acetic acid).

B. Preparation of 1-diazo-3,3-dimethyl-2-butanone

To the diazomethane solution at 0 °C was added a solution of 1.23 mL (1.21 g, 10 mmol, Aldrich) of trimethylacetyl chloride in 1 mL of diethyl ether dropwise with stirring. The resulting mixture was kept at 0 °C for 16 h. The solution was sparged with argon to remove the excess diazomethane and diethyl ether was removed under reduced pressure to give 1.33 g (10 mmol, 100%) of crude 1-diazo-3,3-dimethyl-2-butanone as a yellow liquid.

C. Preparation of 2-chloromethyl-5-t-butyloxazole

To a solution of 2 mL (2.3 g, 16 mmol) of boron trifluoride etherate in 20 mL of chloroacetonitrile at 0 °C was added a solution of 1.33 g (10 mmol) of 1-diazo-3,3-dimethyl-2-butanone in 5 mL of chloroacetonitrile dropwise. The resulting solution was stirred at 0 °C for 0.5 h. The reaction mixture was added to saturated aqueous sodium bicarbonate solution to neutralize the acid and the product was extracted three times with dichloromethane. The combined extracts was dried (sodium sulfate), concentrated and purified by flash column chromatography (Merck silica, 25 x 200 mm, dichloromethane) to give 1.1 g of 2-(chloromethyl)-5-t-butyloxazole as a yellow liquid (6.4 mmol, 64% overall from the acid chloride).

^1H NMR δ ($CDCl_3$): 1.30 (s, 9H), 4.58 (s, 2H), 6.68 (s, 1H); MS 174 $(M+H)^+$; TLC: R_f (silica gel, dichloromethane)=0.33;

HPLC: t_R (YMC S-3 ODS 4.6x50mm rapid resolution; 2.5 ml/min, gradient 0-100% B over 8 min, Solvent A: 10% CH_3OH/90% H_2O/0.2% H_3PO_4; Solvent B: 90% CH_3OH/10% H_2O/0.2% H_3PO_4; UV: 254 nm)= 6.5 min.

D. Preparation of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide

To a solution of 50 mg (0.23 mmol, Applied Chemical Laboratory) of N-[5-(acetylthio)-2-thiazolyl]acetamide in 10 mL of THF was added 0.25 mL of potassium tert-butoxide solution (1 M solution, 0.25 mmol) at rt under argon. The resulting suspension was stirred for 15 min at rt, then a solution of 59 mg of 2-(chhloromethyl)-5-t-butyloxazole (0.34 mmol) in 1 mL of THF was added. The resulting mixture was stirred at rt for 16 h, concentrated under reduced pressure and purified by flash column chromatography (silica gel, 25 x 200 mm, 1:1 EtOAc/hexanes followed by 100% EtOAc) to give 44 mg (0.14 mmol, 61%) of N-[5-[[(5-t-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide as a white solid.

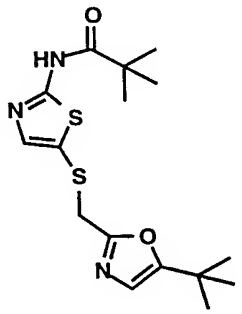
^{1}H NMR δ ($CDCl_3$) 1.27 (s, 9H), 2.27 (s, 3H), 3.95 (s, 2H), 6.59 (s, 1H), 7.31 (s, 1H), 11.03 (broad s, 1H); MS 312 $(M+H)^+$;

TLC: R_f (silica gel, ethyl acetate)=0.53, UV;

HPLC: retention tim (YMC S-3 ODS 4.6x50mm rapid resolution; 2.5 ml/min, gradient 0-100%B over 8 min, Solvent A: 10% CH_3OH/90% H_2O/0.2% H_3PO_4; Solvent B: 90% CH_3OH/10% H_2O/0.2% H_3PO_4; UV: 254 nm)= 6.8 min.

Example 6

N-[5-[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl] trimethylacetamide



A. Preparation of N-[(5-thiocyanato)-2-thiazolyl] trifluoroacetamide (XVIII)

To a mixture of 5-thiocyanato-2-aminothiazole (30 mmol) and 2,6-lutidine (35 mmol) in tetrahydrofuran (25 mL) and dichloromethane (50 mL) at -78 °C under argon was slowly added trifluoroaceticanhydride (33 mmol). After addition, the mixture was allowed to warm up to rt and stirred overnight. The mixture was diluted with dichloromethane (100 mL), and the organic solution was washed with 5% aqueous citric acid followed by brine, dried over magnesium sulfate and passed through a pad of silica gel. The product containing eluent was concentrated to afford 5.3 g of light brown solid.

^{1}H -NMR ($CDCl_3$) δ 12.4 (br, 1H), 7.83 (s, 1H).

B. Preparation of 4-hydroxymethyl-3-methoxyphenyloxy Merrifield resin (XVI)

To the suspension of sodium hydride (11.7 g, 60% in mineral oil, 293 mmol) in dimethylformamide (30 mL) at 0 °C under argon was slowly added a solution of 4-hydroxy-3-methoxybenzyldehyde (44.5 g, 292.5 mmol) in dimethylformamide (100 mL). To the resulting mixture Merrifield resin (1% DVB, from Advanced Chemtech, loading 1.24 mmol/g, 50 g, 62 mmol) and catalytic amount of tetra-n-butylammonium idodide were added, and it was heated at 65 °C for a day. The resin was filtered, washed with water (2x), 50% dimethylformamide in water (3x), dimethylformamide (2x), and methanol (5x), and dried *in vacuo*. The dried resin (15 g) was treated with sodium borohydride (3.4 g, 90 mmol) in tetrahydrofuran (50 mL) and ehthanol (50 mL) overnight. The resin was filtered, washed with 50% dimethylformamide in water (3x), dimethylformamide (2x), methanol (2x), and dichloromethane (5x), and dried *in vacuo*.

C. Preparation of 4-chloromethyl-3-methoxyphenyloxy Merrifield resin (XVII)

To a solution of triphenylphosphine (17 g, 65 mmol) in dichloromethane (200 mL) at 0 °C was slowly added triphosgene (9.2 g, 31 mmol) portionwise over a period of 30 minutes. After addition, the reaction mixture was stirred at 0 °C for 10 minutes. The solvent was removed *in vacuo* and the residue was redissolved in dichloromethane (200 mL). To this mixture was added 4-hydroxymethyl-3-methoxyphenyloxy Merrifield resin (12 g). The resulting mixture was agitated for 4 h. The resin was washed with dry dichloromethane (6x) and dried *in vacuo*.

D. Preparation of 4-[N-[(5-thiocyanato)-2-thiazolyltrifluoroacetamido]methyl]-3-methoxyphenyloxy Merrifield resin (XIX)

A mixture of 4-chloromethyl-3-methoxyphenyloxy Merrifield resin (15g), N-[(5-thiocyanato)-2-thiazolyl]trifluoroacetamide (14 g, 55.3 mmol)

and diisopropylethylamine (7.8 mL, 45 mmol) in dimethylformamide (50 mL) and dichloromethane (100 mL) was agitated overnight. The resin was washed with dimethylformamide (2x), methanol (2x), dichloromethane (4x), and dried *in vacuo*.

E. Preparation of 4-[[N-[(5-mercapto)-2-thiazolyl] trifluoroacetamido]methyl]-3-methoxyphenyloxy Merrifield resin (XX)

A mixture of 4-[N-[(5-thiocyanato)-2-thiazolyltrifluoroacetamido] methyl]-3-methoxyphenyloxy Merrifield resin (**XIX**, 18.5 g) and dithiothreitol (12 g, 78 mmol) in tetrahydrofuran (100 mL) and methanol (100 mL) was agitated overnight. The resin was washed with dimethylformamide (2x), methanol (2x), dichloromethane (4x), and dried *in vacuo* and stored under argon at -20 °C.

F. Preparation of 4-N-[5-[[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trifluoroacetamido]methyl-3-methoxyphenyloxy Merrifield resin (XXI)

A stream of argon was bubbled through a mixture 4-[[N-[(5-Mercapto)-2-thiazolyl]trifluoroacetamido]methyl]-3-methoxyphenyloxy Merrifield resin (**XX**, 500 mg), halide (2.0 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 1.5 mmol) in dimethylformamide (3 mL) for 5 min., and the mixture was heated at 80 °C for 2 h. The resin was washed with dimethylformamide (2x), methanol (2x), dichloromethane (4x), and dried *in vacuo*.

G. Preparation of 4-N-[5-[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]methyl-3-methoxyphenyloxy Merrifield resin (XXII)

A mixture of 4-N-[5-[[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trifluoroacetamido]methyl-3-methoxyphenyloxy Merrifield resin (**XXI**, 500 mg) and sodium borohydride (4 mmol) in tetrahydrofuran (2 mL) and ethanol (2 mL) was agitated overnight. The resin was washed with 50% dimethylformamide in water (2x),

dimethylformamide (2x), methanol (2x), dichloromethane (4x), and dried *in vacuo*.

H. Preparation of 4-N-[5-[[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trimethylacetamido]methyl-3-methoxyphenyloxy Merrifield resin (XXIII)

A mixture of 4-N-[5-[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]methyl-3-methoxyphenyloxy Merrifield resin (**XXII**, 100 mg), diisopropylethylamine (1.2 mmol) and trimethylacetyl chloride (1 mmol) in dichloromethane (2 mL) in a polypropylene tube fitted with a polyethylene frit and a luer stopcock was agitated overnight. The resin was washed with dimethylformamide (2x), methanol (2x), dichloromethane (4x), and used in the next step without drying.

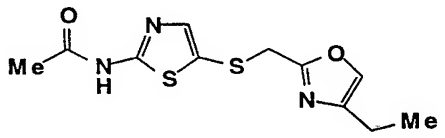
I. Preparation of N-[5-[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trimethylacetamide

4-N-[5-[[[(5-*t*-butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trimethylacetamido]methyl-3-methoxyphenyloxy Merrifield resin (**XXIII**) was treated with 60% trifluoroacetic acid in dichloromethane (2 mL) in a polypropylene tube fitted with a polyethylene frit and a luer stopcock for 4 hours. The solution was decanted to a tube and the resin was washed with dichloromethane. The combined organic solution was concentrated in Speed Vac. The residue was purified by preparative-HPLC to afford 11.3 mg of the desired product.

MS m/e 354 $(M+H)^+$.

Example 7

N-[5-[[(4-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide



A. Preparation of 2-(2-chloroacetamido)-1-butanol

To a mixture of 2-amino-1-butanol (5.0 mL, 53 mmol) and triethyl amine (15.0 mL, 111 mmol) in dichloromethane (20 mL) at -70 °C was added chloroacetyl chloride (4.6 mL, 58 mmol) dropwise. The reaction mixture was stirred at -70 °C for 15 min. and then was allowed to warm to rt. It was diluted with EtOAc (50 mL) and the reaction was quenched by adding water (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers was concentrated to afford 2-(2-chloroacetamido)-1-butanol (8.6 g, 98%) as a brown solid.

^{1}H NMR ($CDCl_3$) δ 6.75 (bs, 1 H), 4.10 (s, 2 H), 4.08(dd, 1H), 3.90 (m, 1 H), 3.68 (m, 2H), 2.98(bs, 1H), 1.60(m, 2H), 0.97 (t, 3H).

B. Preparation of 2-(2-chloroacetamido)-1-butyraldehyde

To a solution of oxalyl chloride (14.5 mL, 29.0 mmol) in dichrolomethane (30 mL) at -78 °C DMSO (2.75 mL, 38.8 mmol) was added dropwise over 5 min.. After stirring for 10 min. at -78 °C, here was added a solution of 2-(2-chloroacetamido)-1-butanol (4.0 g, 24 mmol) in 20 mL of dichrolomethane dropwise over 15 min. The reaction mixture was stirred for 40 min. at -78 °C and here was added triethyl amine (9.4 mL, 68 mmol) dropwise over 5 min. and the reaction mixture was allowed to warm to room temperature and stirred for 2 hrs. The solid was removed by filtration and washed with EtOAc. The organic phase was washed with 1N HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (1 x 10 mL) and concentrated to afford 2-(2-chloroacetamido)-1-butyraldehyde (3.7 g, 95%) as a brown oil.

^{1}H NMR ($CDCl_3$) δ 9.60 (s, 1 H), 4.52 (q, 1 H), 4.12(s, 2H), 2.05 (m, 1 H), 1.80 (m, 1H), 0.97 (t, 3H).

C. Preparation of 2-chloromethy-4-ethyloxazole

To a solution of 2-(2-chloroacetamido)-1-butyraldehyde (3.7 g, 23 mmol) in toluene (10 mL) was added $POCl_3$ (6.3 mL, 68 mmol). The reaction mixture was heated at 90 °C for 1 h under nitrogen. After cooling the reaction mixture to room temperature it was poured into ice water (10 mL) and the pH of the solution was adjusted to 7 with 5N NaOH. The toluene layer was separated and the aqueous layer was washed with dichloromethane (3 x 20 mL). The combined organic solution was concentrated and distilled to afford 2-chloromethy-4-ethyloxazole (1.1g, 31%) as a colorless liquid.

^{1}H NMR ($CDCl_3$) δ 7.30 (s, 1H), 4.22 (s, 2 H), 2.50 (q, 2 H), 1.22 (t, 3H).

D. Preparation of N-[5-[[(4-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide

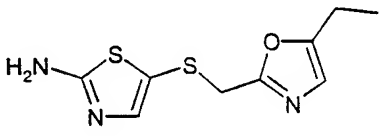
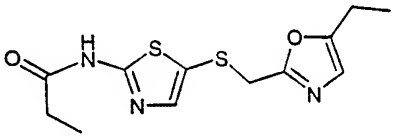
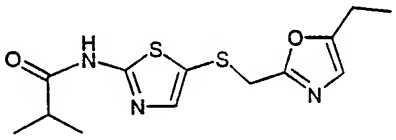
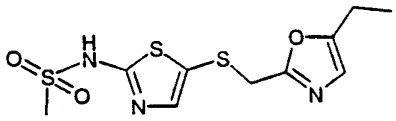
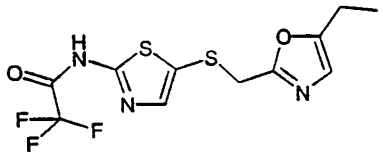
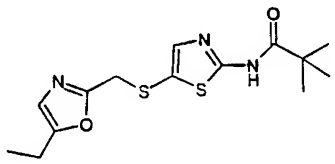
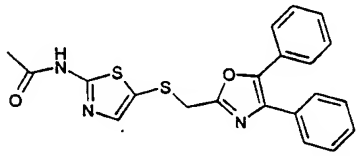
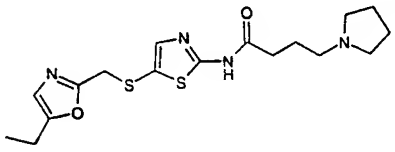
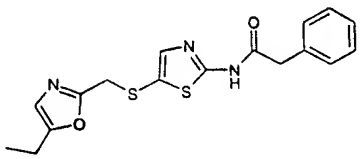
To a solution of 2-acetylamino-5-thiazolylthiol (0.010 g, 0.050 mmol) in dry THF (5 mL) was added potassium *tert*-butoxide (1.0 M solution in THF, 0.060 mL, 0.060 mmol). The reaction mixture was stirred at room temperature for 15 min. and here was added 2-chloromethyl-4-ethyloxazole (0.015 g, 0.10 mmol). After 3 h, saturated aqueous $NaHCO_3$ solution (5 mL) was added to the mixture. The organic layer was separated and the aqueous layer was washed with dichloromethane (3 x 10 mL). The combined organic layers was concentrated. The residue was purified by flash chromatography (SiO_2; methanol:dichloromethane /1:20) to afford N-[5-[[(4-ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide (5 mg, 36%) as a white solid.

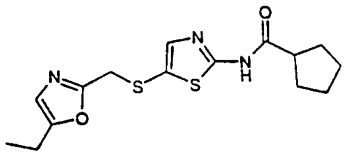
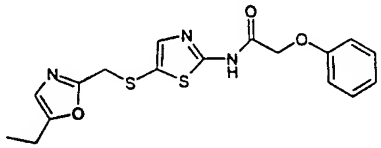
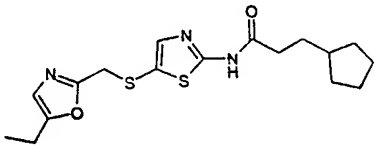
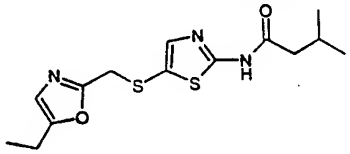
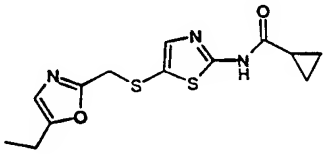
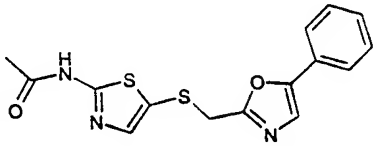
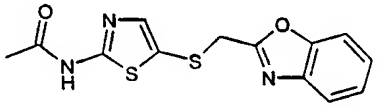
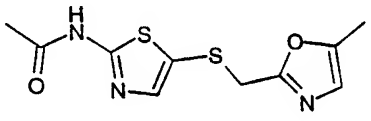
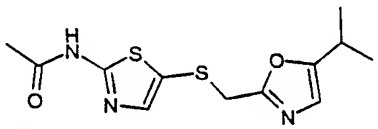
^{1}H NMR ($CDCl_3$) δ 11.25 (s, 1 H), 7.34 (s, 1 H), 7.31(s, 1H), 3.95 (s, 2 H), 2.50 (q, 2H), 2.27(s, 3H), 1.19 (t, 3H); MS m/e 284 $(M+H)^+$; HPLC (Column: Zorbax Rapid resolution C-18; flow rate: 2.5 ml/min; solvent system: 0-100% B in 8 min. Solvent A: 10% CH_3OH/90% H_2O/0.2% H_3PO_4;

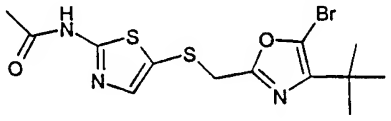
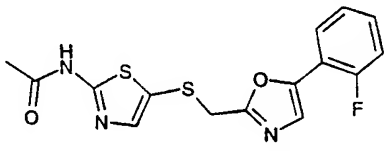
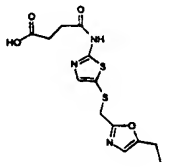
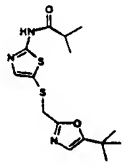
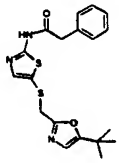
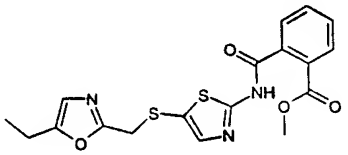
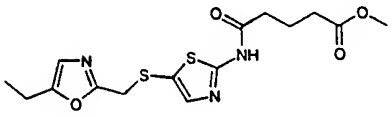
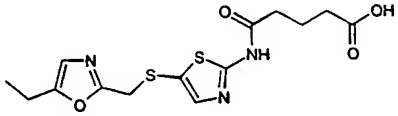
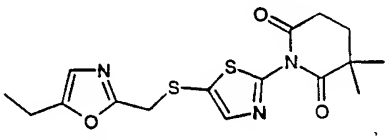
Solvent B: 90% CH_3OH/10% H_2O/0.2% H_3PO_4; UV: 254 nm): retention time 6.14 min.

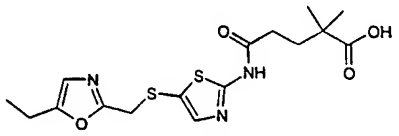
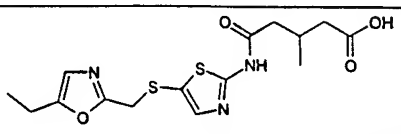
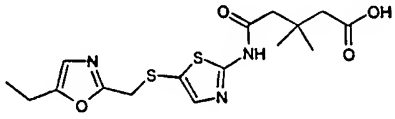
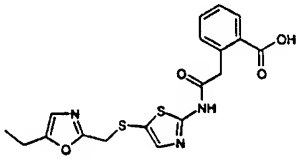
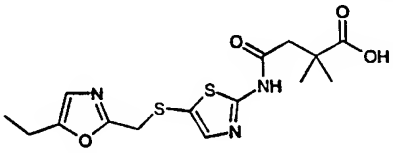
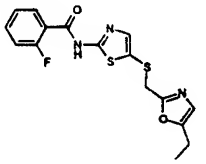
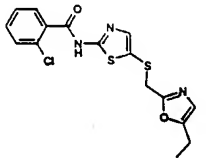
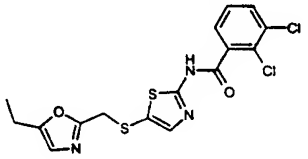
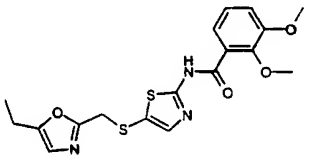
Using the procedures described herein or by modification of the procedures described herein as known to one or ordinary skill in the art, the following additional compounds have been prepared and disclosed in Table 1:

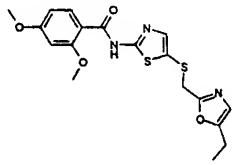
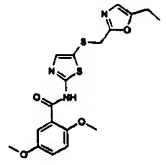
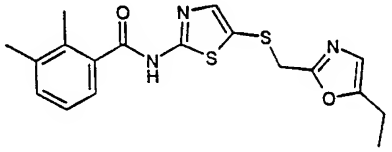
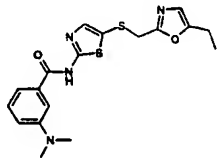
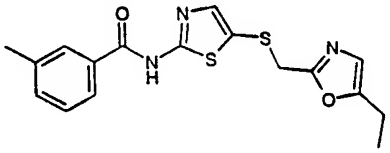
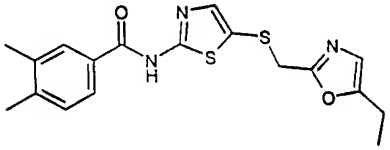
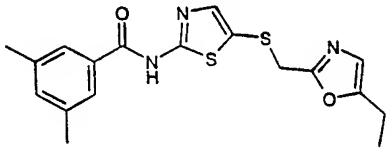
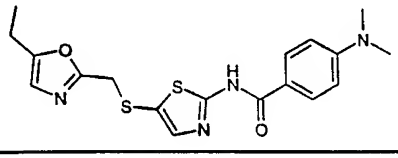
TABLE 1

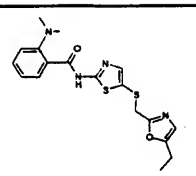
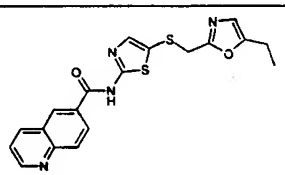
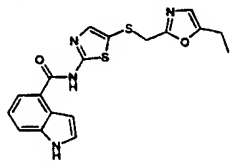
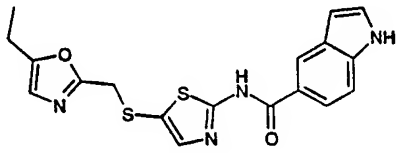
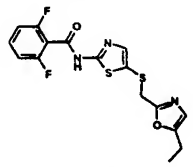
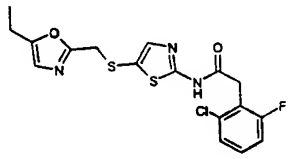
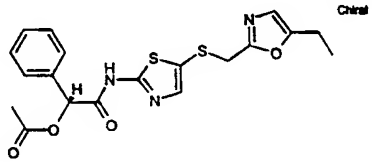
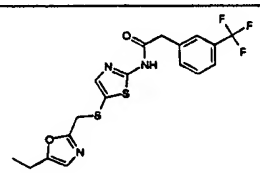
Example	Structure	Molecular Formula	(M+H)+
8		C9H11N3OS2	242
9		C12H15N3O2S2	298
10		C13H17N3O2S2	312
11		C10H13N3O3S3	320
12		C11H10F3N3O2S2	338
13		C14H19N3O2S2	326
14		C21H17N3O2S2	408
15		C17H24N4O2S2	381
16		C17H17N3O2S2	360

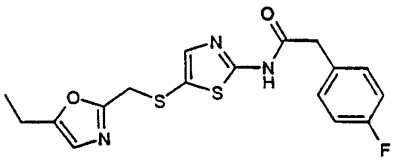
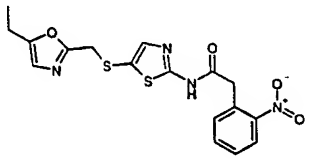
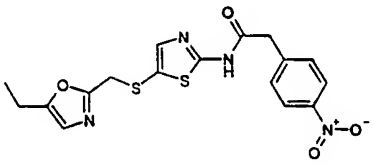
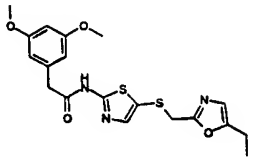
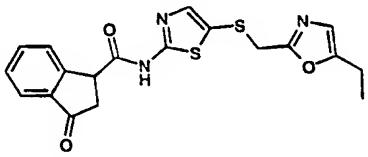
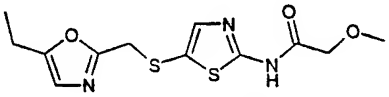
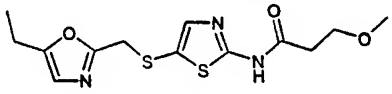
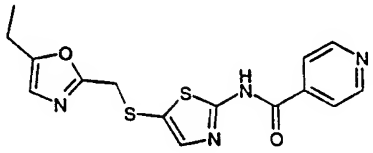
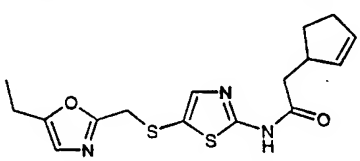
17		C15H19N3O2S2	338
18		C17H17N3O3S2	376
19		C17H23N3O2S2	366
20		C14H19N3O2S2	326
21		C13H15N3O2S2	310
22		C15H13N3O2S2	332
23		C13H11N3O2S2	306
24		C10H11N3O2S2	270
25		C12H15N3O2S2	298

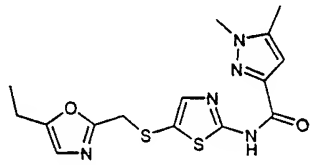
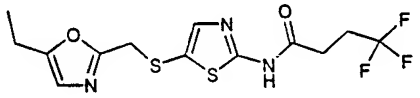
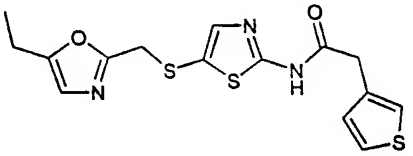
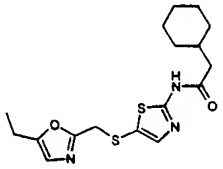
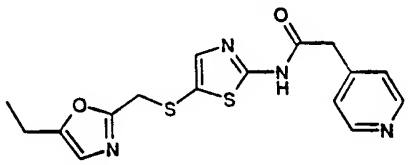
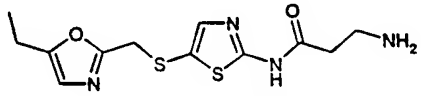
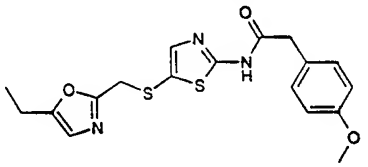
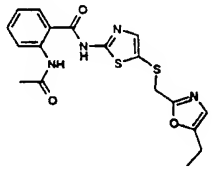
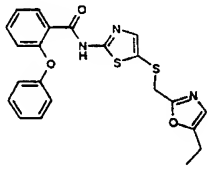
26		C13H16BrN3O2S2	391
27		C15H12FN3O2S2	350
28		C13H15N3O4S2	342
29		C15 H21 N3 O2 S2	340
30		C19H21N3O2S2	388
31		C18H17N3O4S2	404
32		C15H19N3O4S2	370
33		C14H17N3O4S2	356
34		C16H19N3O3S2	366

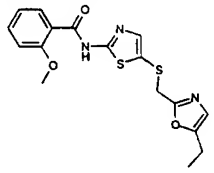
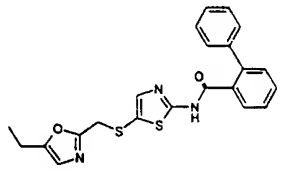
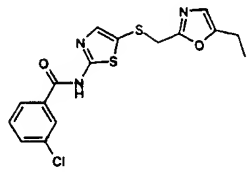
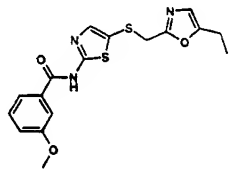
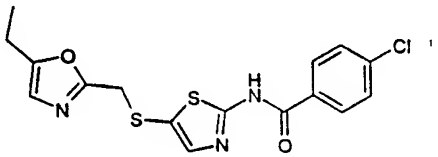
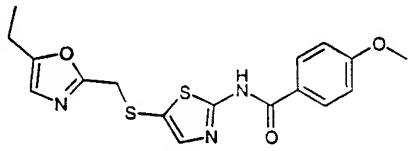
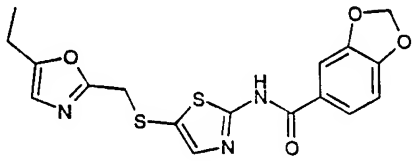
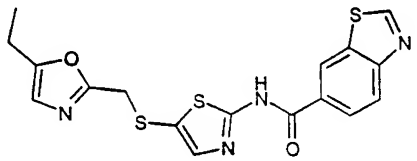
35		C16H21N3O4S2	384
36		C15H19N3O4S2	370
37		C16H21N3O4S2	384
38		C18 H17 N3 O4 S2	404
39		C15H19N3O4S2	370
40		C16 H14 F N3 O2 S2	364
41		C16 H14 Cl N3 O2 S2	380
42		C16 H13 Cl2 N3 O2 S2	415
43		C18 H19 N3 O4 S2	406

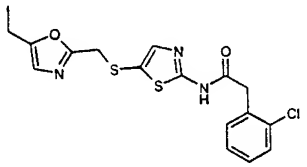
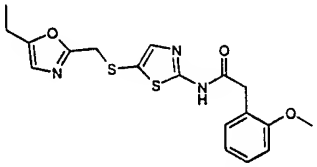
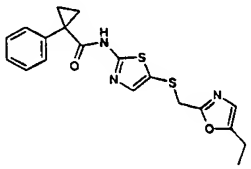
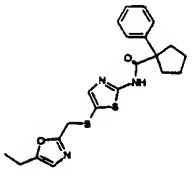
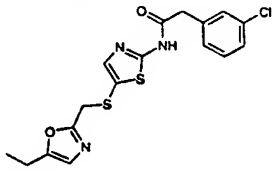
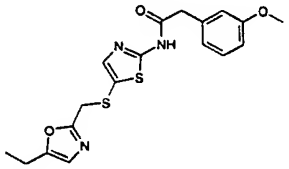
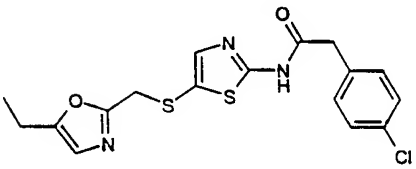
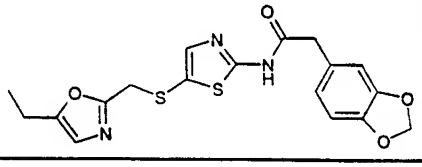
44		C18 H19 N3 O4 S2	406
45		C18 H19 N3 O4 S2	406
46		C18 H19 N3 O2 S2	374
47		C18 H20 N4 O2 S2	503
48		C17 H17 N3 O2 S2	360
49		C18 H19 N3 O2 S2	374
50		C18 H19 N3 O2 S2	374
51		C18 H20 N4 O2 S2	503

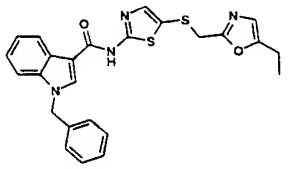
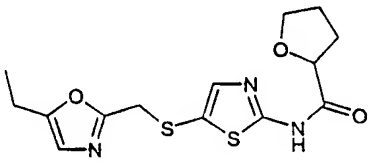
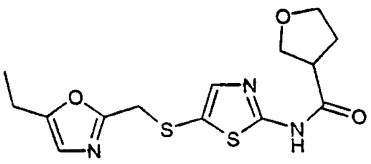
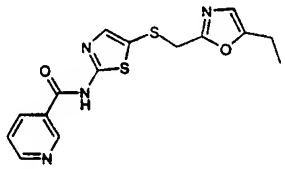
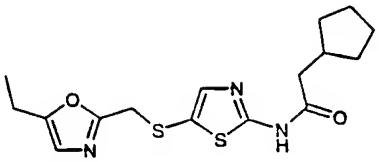
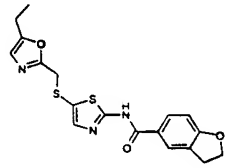
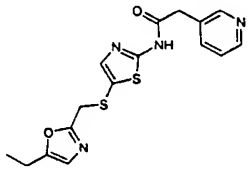
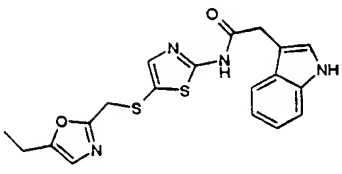
52		C18 H20 N4 O2 S2	503
53		C19 H16 N4 O2 S2	511
54		C18 H16 N4 O2 S2	499
55		C18 H16 N4 O2 S2	499
56		C16 H13 F2 N3 O2 S2	382
57		C17 H15 Cl F N3 O2 S2	412
58		C19 H19 N3 O4 S2	418
59		C18 H16 F3 N3 O2 S2	428

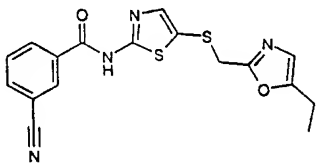
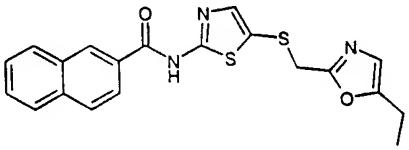
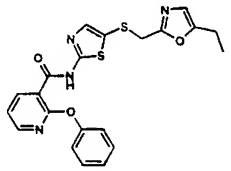
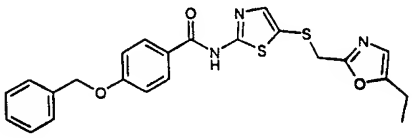
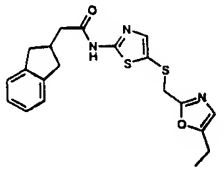
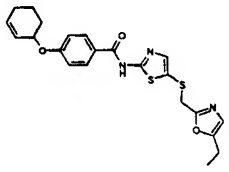
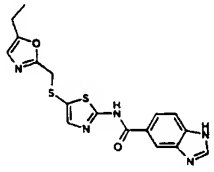
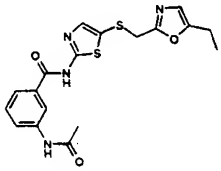
60		C17 H16 F N3 O2 S2	378
61		C17 H16 N4 O4 S2	405
62		C17 H16 N4 O4 S2	405
63		C19 H21 N3 O4 S2	420
64		C19 H17 N3 O3 S2	400
65		C12 H15 N3 O3 S2	314
66		C13 H17 N3 O3 S2	328
67		C15 H14 N4 O2 S2	461
68		C16 H19 N3 O2 S2	350

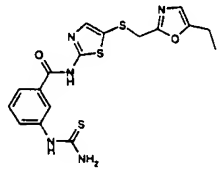
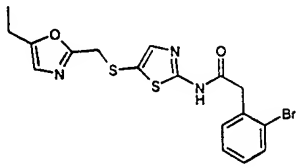
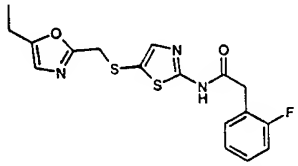
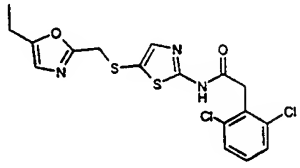
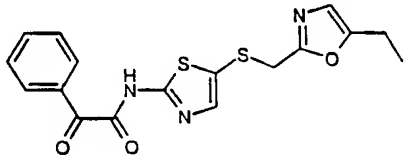
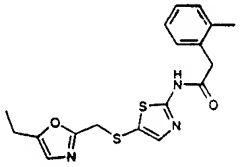
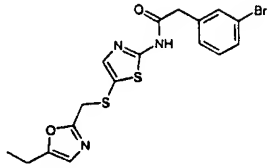
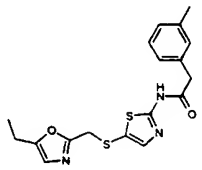
69		C15 H17 N5 O2 S2	364
70		C13 H14 F3 N3 O2 S2	366
71		C15 H15 N3 O2 S3	366
72		C17 H23 N3 O2 S2	366
73		C16 H16 N4 O2 S2	475
74		C12 H16 N4 O2 S2	427
75		C18 H19 N3 O3 S2	390
76		C18 H18 N4 O3 S2	403
77		C22 H19 N3 O3 S2	438

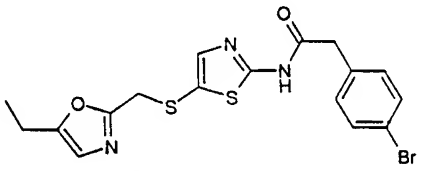
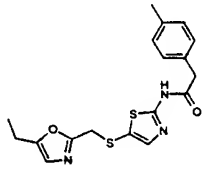
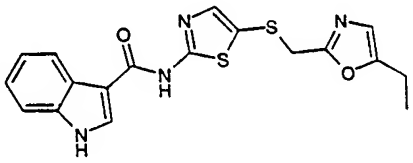
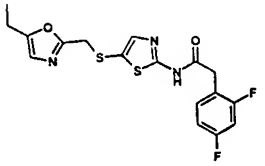
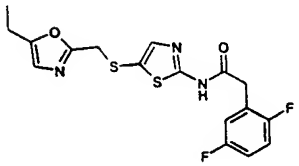
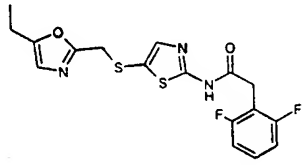
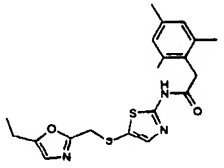
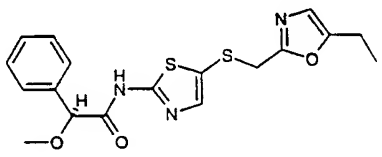
78		C17 H17 N3 O3 S2	376
79		C22 H19 N3 O2 S2	422
80		C16 H14 Cl N3 O2 S2	380
81		C17 H17 N3 O3 S2	376
82		C16 H14 Cl N3 O2 S2	380
83		C17 H17 N3 O3 S2	376
84		C17 H15 N3 O4 S2	390
85		C17 H14 N4 O2 S3	403

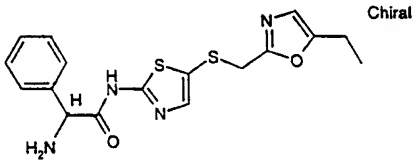
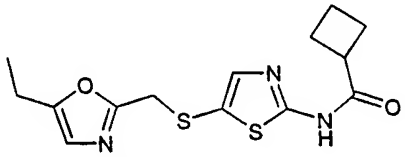
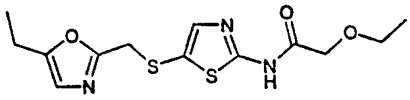
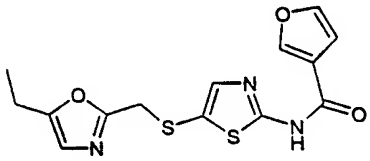
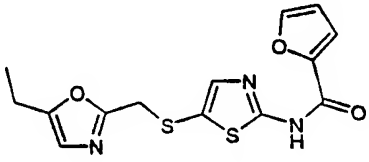
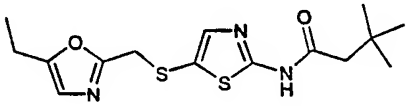
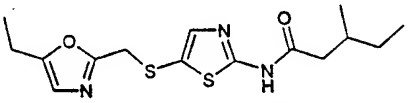
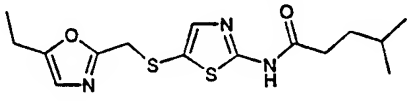
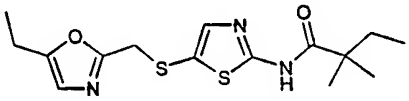
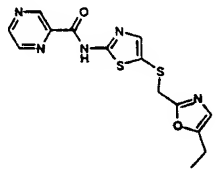
86		C17 H16 Cl N3 O2 S2	394
87		C18 H19 N3 O3 S2	390
88		C19 H19 N3 O2 S2	386
89		C21 H23 N3 O2 S2	414
90		C17 H16 Cl N3 O2 S2	394
91		C18 H19 N3 O3 S2	390
92		C17 H16 Cl N3 O2 S2	394
93		C18 H17 N3 O4 S2	404

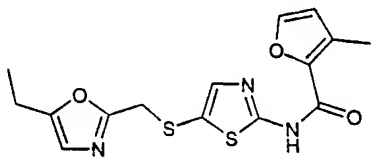
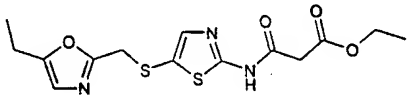
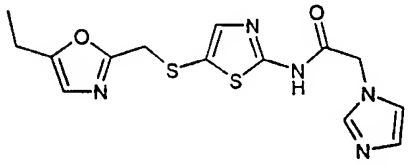
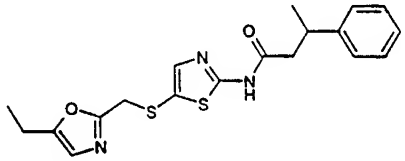
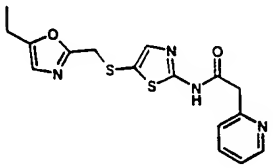
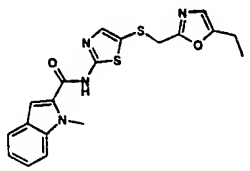
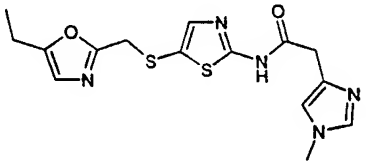
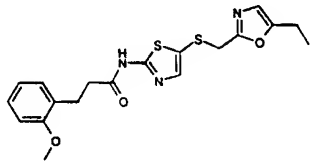
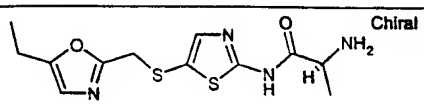
94		C25 H22 N4 O2 S2	589
95		C14 H17 N3 O3 S2	340
96		C14 H17 N3 O3 S2	340
97		C15 H14 N4 O2 S2	461
98		C16 H21 N3 O2 S2	352
99		C18 H17 N3 O3 S2	388
100		C16 H16 N4 O2 S2	475
101		C19 H18 N4 O2 S2	513

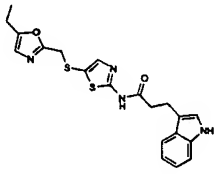
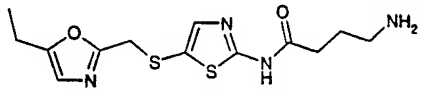
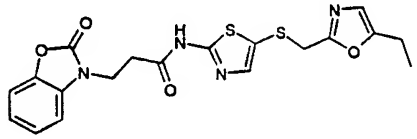
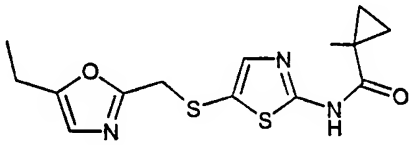
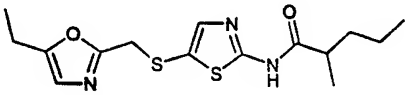
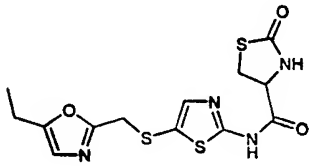
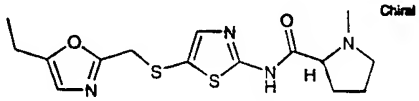
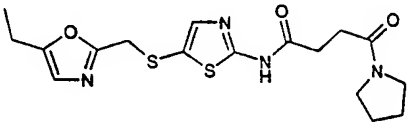
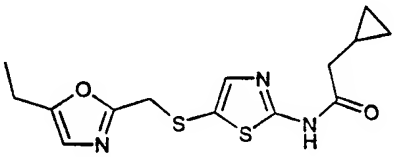
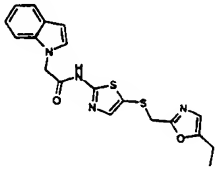
102		C17 H14 N4 O2 S2	371
103		C20 H17 N3 O2 S2	396
104		C21 H18 N4 O3 S2	553
105		C23 H21 N3 O3 S2	452
106		C20 H21 N3 O2 S2	400
107		C22 H23 N3 O3 S2	442
108		C17 H15 N5 O2 S2	500
109		C18 H18 N4 O3 S2	403

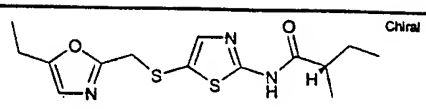
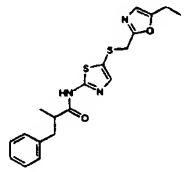
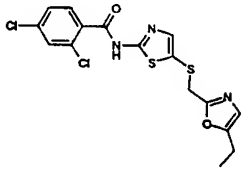
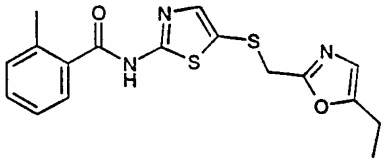
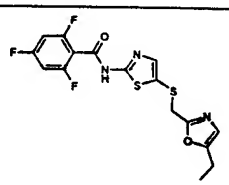
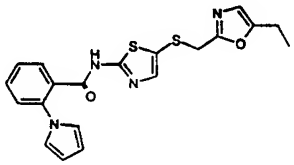
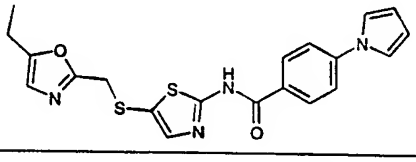
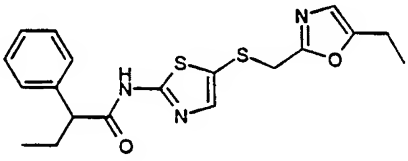
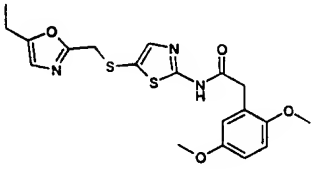
110		C17 H17 N5 O2 S3	420
111		C17 H16 Br N3 O2 S2	439
112		C17 H16 F N3 O2 S2	378
113		C17 H15 Cl2 N3 O2 S2	429
114		C17 H15 N3 O3 S2	374
115		C18 H19 N3 O2 S2	374
116		C17 H16 Br N3 O2 S2	439
117		C18 H19 N3 O2 S2	374

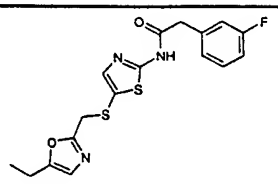
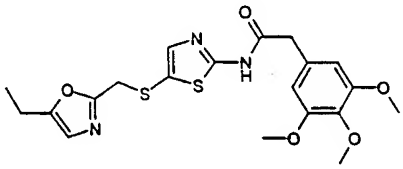
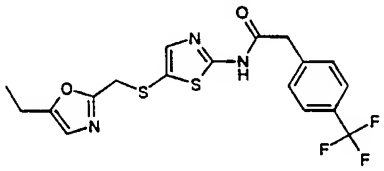
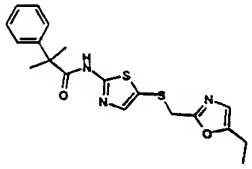
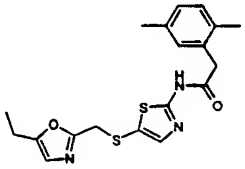
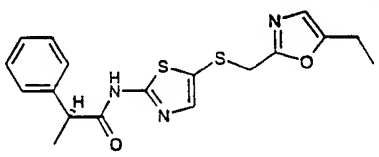
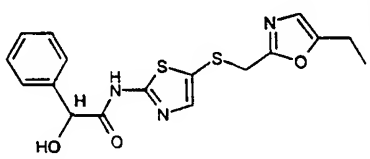
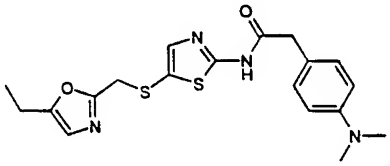
118		C17 H16 Br N3 O2 S2	439
119		C18 H19 N3 O2 S2	374
120		C18 H16 N4 O2 S2	499
121		C17 H15 F2 N3 O2 S2	396
122		C17 H15 F2 N3 O2 S2	396
123		C17 H15 F2 N3 O2 S2	396
124		C20 H23 N3 O2 S2	402
125	 Chiral	C18 H19 N3 O3 S2	390

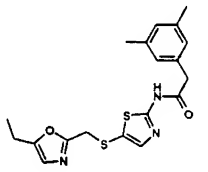
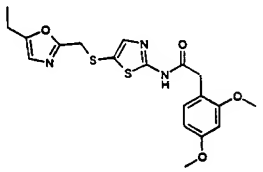
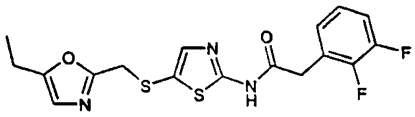
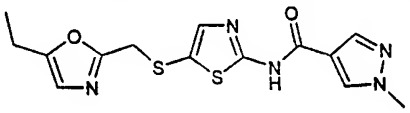
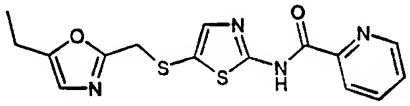
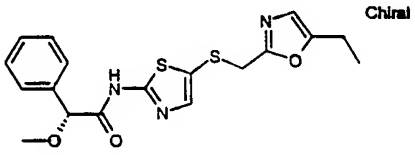
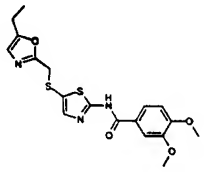
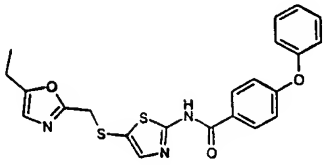
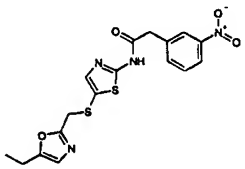
126		C17 H18 N4 O2 S2	489
127		C14 H17 N3 O2 S2	324
128		C13 H17 N3 O3 S2	328
129		C14 H13 N3 O3 S2	336
130		C14 H13 N3 O3 S2	336
131		C15 H21 N3 O2 S2	340
132		C15 H21 N3 O2 S2	340
133		C15 H21 N3 O2 S2	340
134		C15 H21 N3 O2 S2	340
135		C14 H13 N5 O2 S2	348

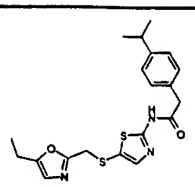
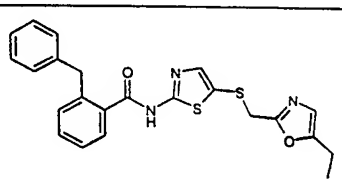
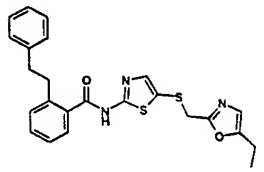
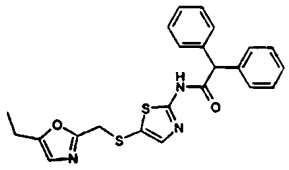
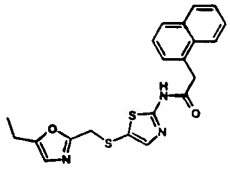
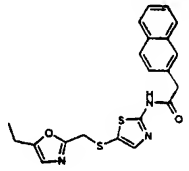
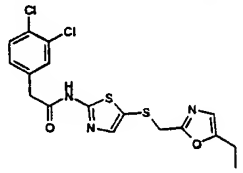
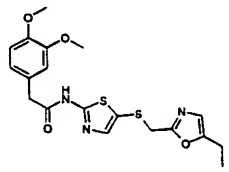
136		C15 H15 N3 O3 S2	**350**
137		C14 H17 N3 O4 S2	**356**
138		C14 H15 N5 O2 S2	**464**
139		C19 H21 N3 O2 S2	**388**
140		C16 H16 N4 O2 S2	**475**
141		C19 H18 N4 O2 S2	**513**
142		C15 H17 N5 O2 S2	**478**
143		C19 H21 N3 O3 S2	**404**
144	 Chiral	C12 H16 N4 O2 S2	**427**

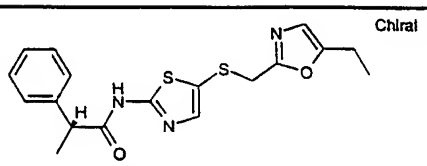
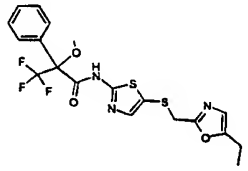
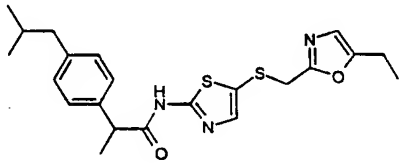
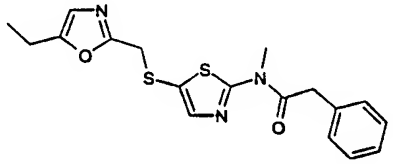
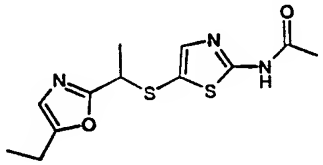
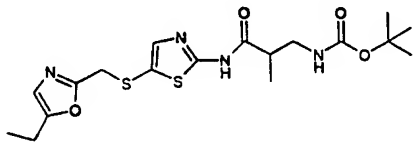
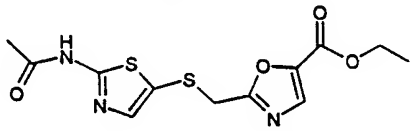
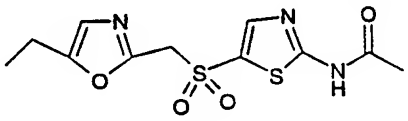
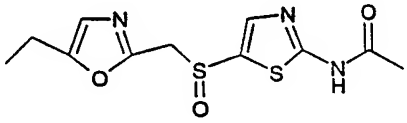
145		C20 H20 N4 O2 S2	527
146		C13 H18 N4 O2 S2	441
147		C19 H18 N4 O4 S2	431
148		C14 H17 N3 O2 S2	324
149		C15 H21 N3 O2 S2	340
150		C13 H14 N4 O3 S3	371
151		C15 H20 N4 O2 S2	467
152		C17 H22 N4 O3 S2	395
153		C14 H17 N3 O2 S2	324
154		C19 H18 N4 O2 S2	513

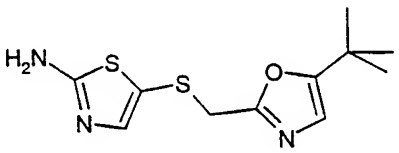
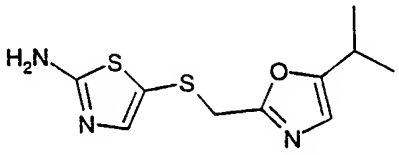
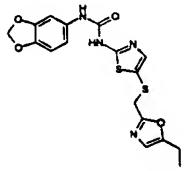
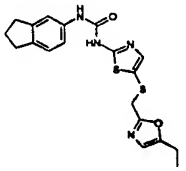
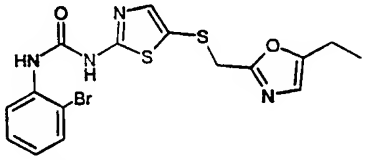
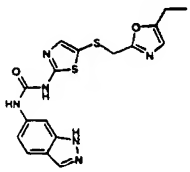
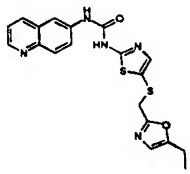
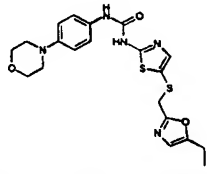
155		C14 H19 N3 O2 S2	326
156		C19 H21 N3 O2 S2	388
157		C16 H13 Cl2 N3 O2 S2	415
158		C17 H17 N3 O2 S2	360
159		C16 H12 F3 N3 O2 S2	400
160		C20 H18 N4 O2 S2	525
161		C20 H18 N4 O2 S2	525
162		C19 H21 N3 O2 S2	388
163		C19 H21 N3 O4 S2	420

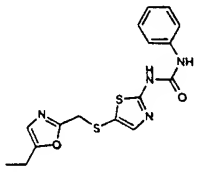
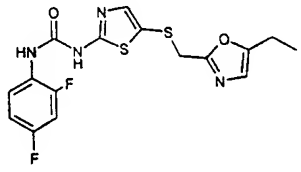
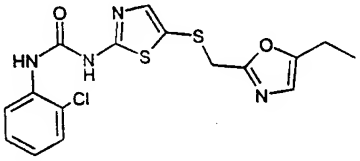
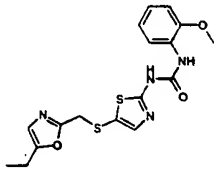
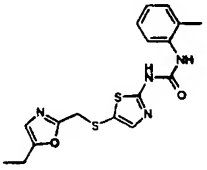
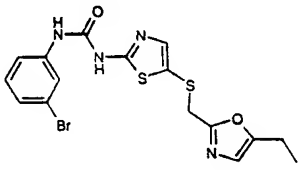
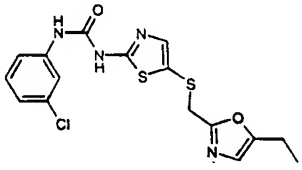
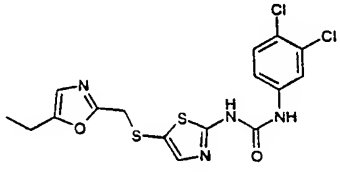
164		C17 H16 F N3 O2 S2	378
165		C20 H23 N3 O5 S2	450
166		C18 H16 F3 N3 O2 S2	428
167		C19 H21 N3 O2 S2	388
168		C19 H21 N3 O2 S2	388
169	 Chiral	C18 H19 N3 O2 S2	374
170	 Chiral	C17 H17 N3 O3 S2	376
171		C19 H22 N4 O2 S2	517

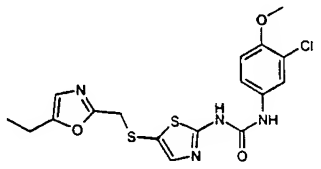
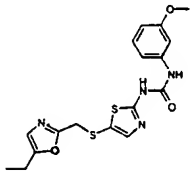
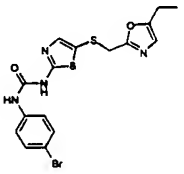
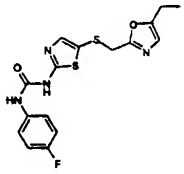
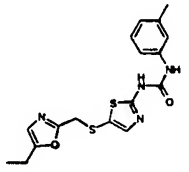
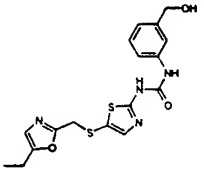
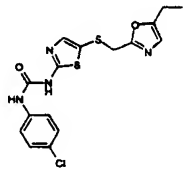
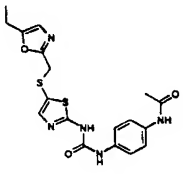
172		C19 H21 N3 O2 S2	388
173		C19 H21 N3 O4 S2	420
174		C17 H15 F2 N3 O2 S2	396
175		C14 H15 N5 O2 S2	350
176		C15 H14 N4 O2 S2	461
177	 Chiral	C18 H19 N3 O3 S2	390
178		C18 H19 N3 O4 S2	406
179		C22 H19 N3 O3 S2	438
180		C17 H16 N4 O4 S2	405

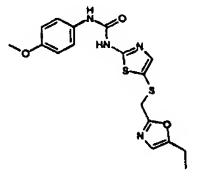
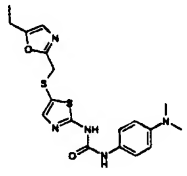
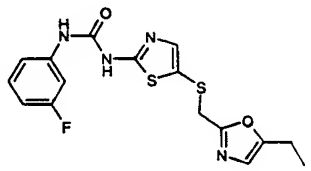
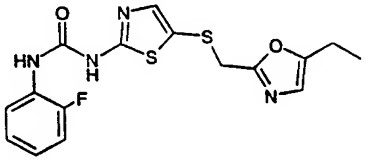
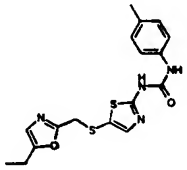
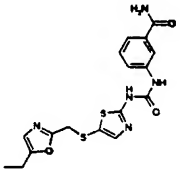
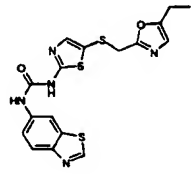
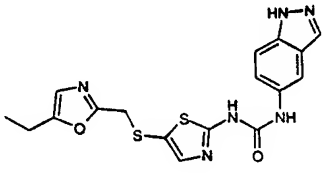
181		C20 H23 N3 O2 S2	402
182		C23 H21 N3 O2 S2	436
183		C24 H23 N3 O2 S2	450
184		C23 H21 N3 O2 S2	436
185		C21 H19 N3 O2 S2	410
186		C21 H19 N3 O2 S2	410
187		C17 H15 Cl2 N3 O2 S2	429
188		C19 H21 N3 O4 S2	420

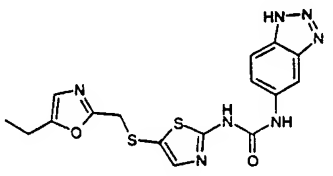
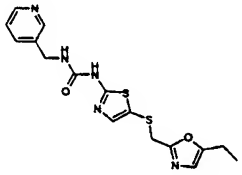
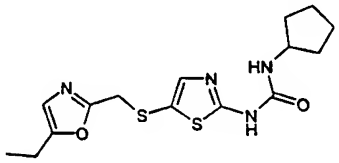
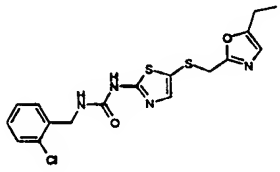
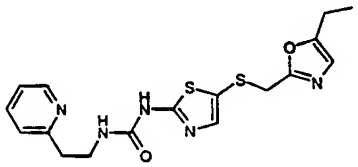
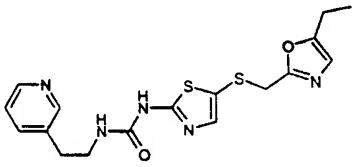
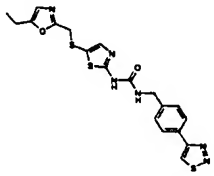
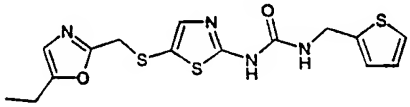
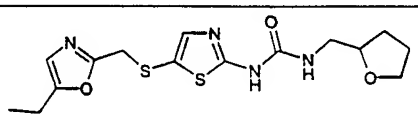
189		C18 H19 N3 O2 S2	374
190		C19 H18 F3 N3 O3 S2	458
191		C22 H27 N3 O2 S2	430
192		C18 H19 N3 O2 S2	374
193		C12 H15 N3 O2 S2	298
194		C18 H26 N4 O4 S2	427
195		C12 H13 N3 O4 S2	328
196		C11 H13 N3 O4 S2	316
197		C11 H13 N3 O3 S2	300

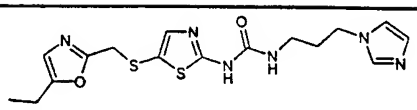
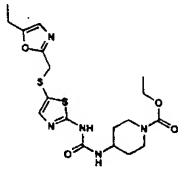
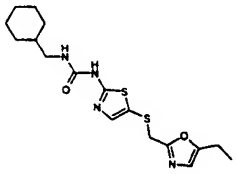
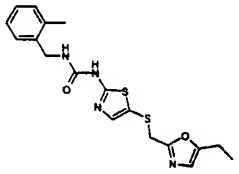
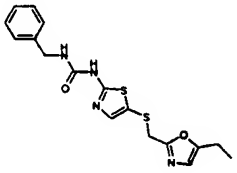
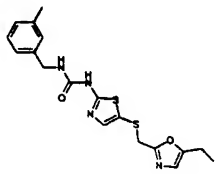
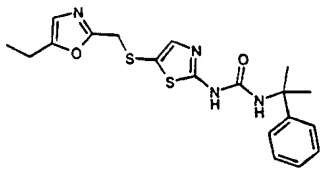
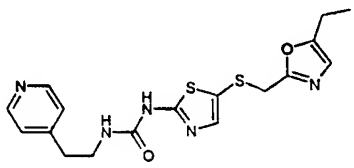
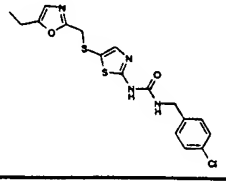
198		C11 H15 N3 O S2	270
199		C10 H13 N3 O S2	256
200		C17 H16 N4 O4 S2	405
201		C19 H20 N4 O2 S2	401
202		C16 H15 Br N4 O2 S2	440
203		C17 H16 N6 O2 S2	515
204		C19 H17 N5 O2 S2	526
205		C20 H23 N5 O3 S2	560

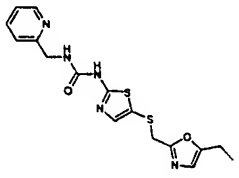
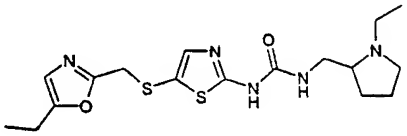
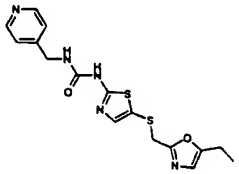
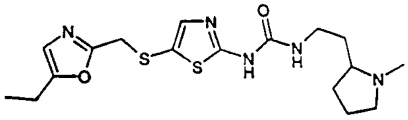
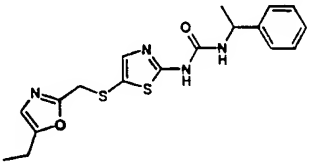
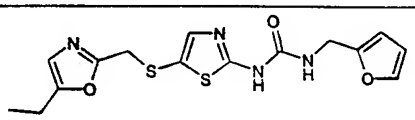
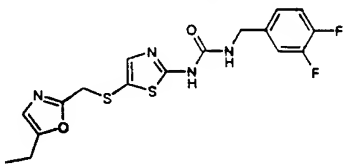
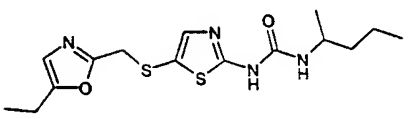
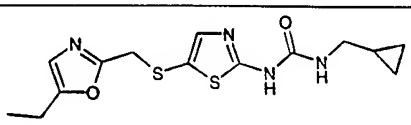
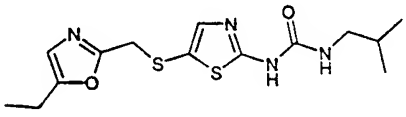
206		C16 H16 N4 O2 S2	361
207		C16 H14 F2 N4 O2 S2	397
208		C16 H15 Cl N4 O2 S2	395
209		C17 H18 N4 O3 S2	391
210		C17 H18 N4 O2 S2	375
211		C16 H15 Br N4 O2 S2	440
212		C16 H15 Cl N4 O2 S2	395
213		C16 H14 Cl2 N4 O2 S2	430

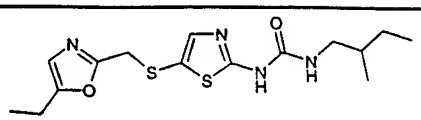
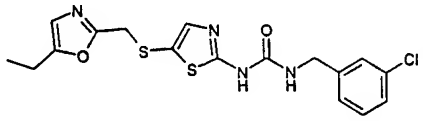
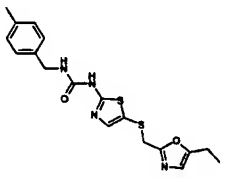
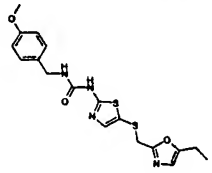
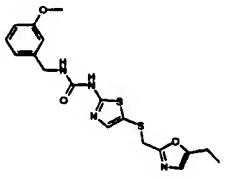
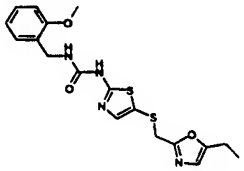
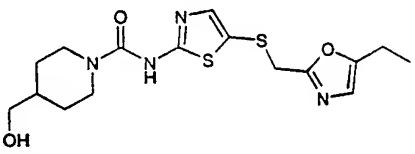
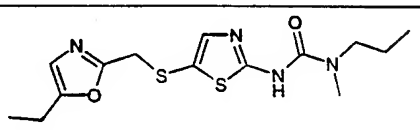
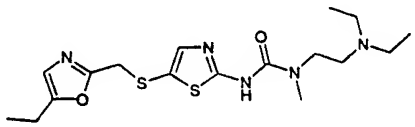
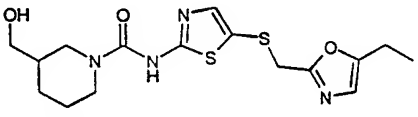
214		C17 H17 Cl N4 O3 S2	425
215		C17 H18 N4 O3 S2	391
216		C16 H15 Br N4 O2 S2	440
217		C16 H15 F N4 O2 S2	379
218		C17 H18 N4 O2 S2	375
219		C17 H18 N4 O3 S2	391
220		C16 H15 Cl N4 O2 S2	395
221		C18 H19 N5 O3 S2	418

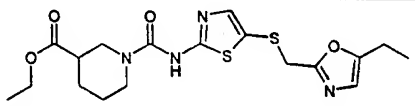
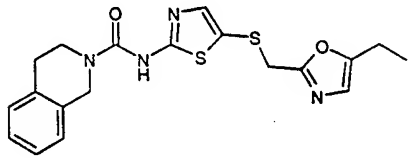
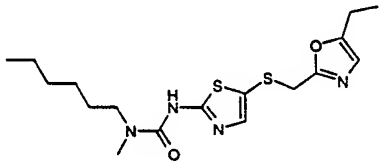
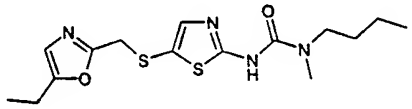
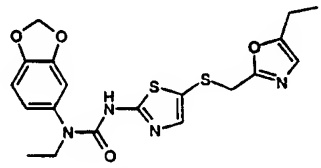
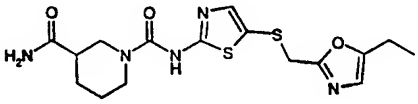
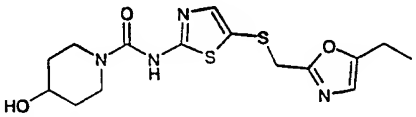
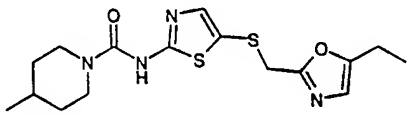
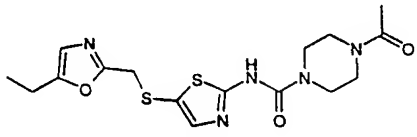
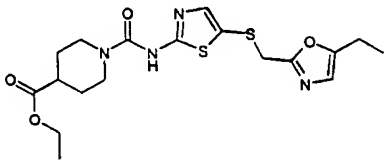
222		C17 H18 N4 O3 S2	391
223		C18 H21 N5 O2 S2	518
224		C16 H15 F N4 O2 S2	379
225		C16 H15 F N4 O2 S2	379
226		C17 H18 N4 O2 S2	375
227		C17 H17 N5 O3 S2	404
228		C17 H15 N5 O2 S3	418
229		C17 H16 N6 O2 S2	401

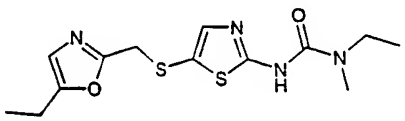
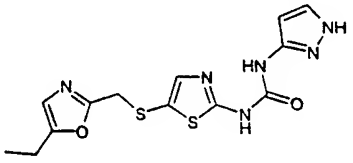
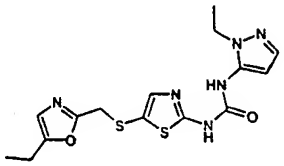
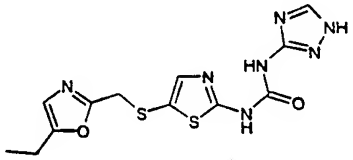
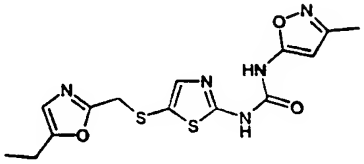
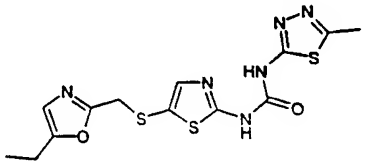
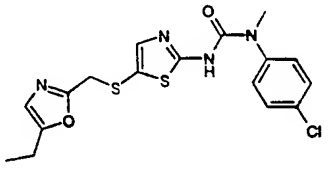
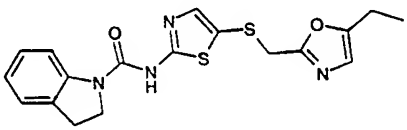
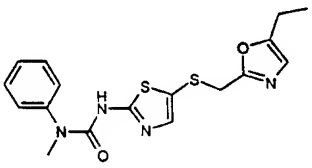
230		C16 H15 N7 O2 S2	402
231		C16 H17 N5 O2 S2	490
232		C15 H20 N4 O2 S2	353
233		C17 H17 Cl N4 O2 S2	409
234		C17 H19 N5 O2 S2	504
235		C17 H19 N5 O2 S2	504
236		C19 H18 N6 O2 S3	459
237		C15 H16 N4 O2 S3	381
238		C15 H20 N4 O3 S2	369

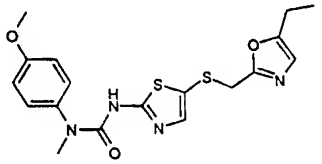
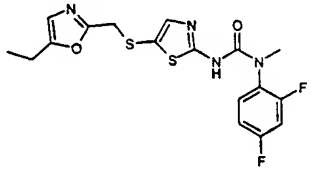
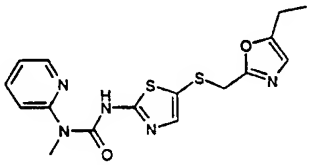
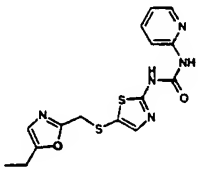
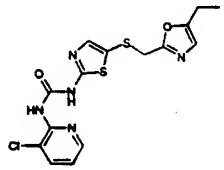
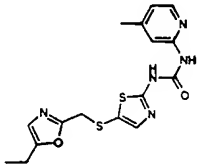
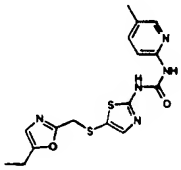
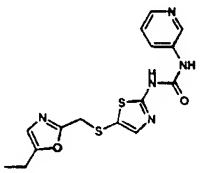
239		C16 H20 N6 O2 S2	507
240		C18 H25 N5 O4 S2	440
241		C17 H24 N4 O2 S2	381
242		C18 H20 N4 O2 S2	389
243		C17 H18 N4 O2 S2	375
244		C18 H20 N4 O2 S2	389
245		C19 H22 N4 O2 S2	403
246		C17 H19 N5 O2 S2	504
247		C17 H17 Cl N4 O2 S2	409

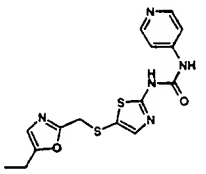
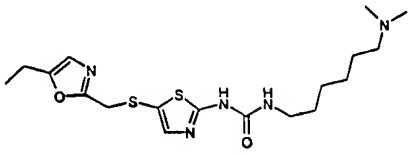
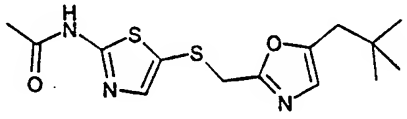
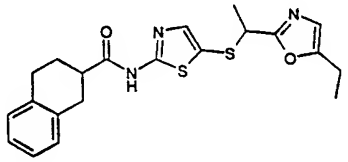
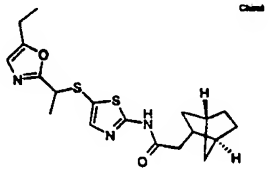
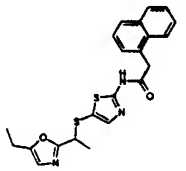
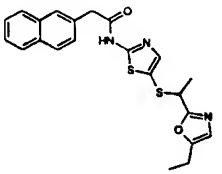
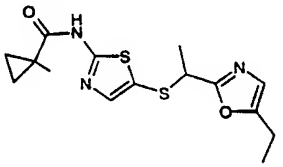
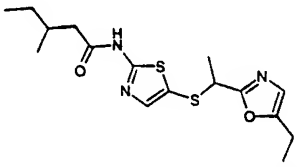
248		C16 H17 N5 O2 S2	490
249		C17 H25 N5 O2 S2	510
250		C16 H17 N5 O2 S2	490
251		C17 H25 N5 O2 S2	510
252		C18 H20 N4 O2 S2	389
253		C15 H16 N4 O3 S2	365
254		C17 H16 F2 N4 O2 S2	411
255		C15 H22 N4 O2 S2	355
256		C14 H18 N4 O2 S2	339
257		C14 H20 N4 O2 S2	341

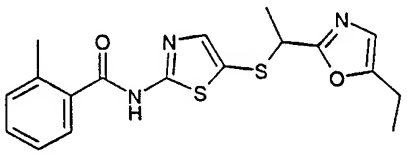
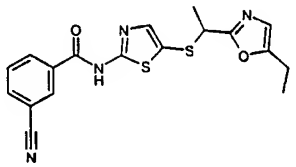
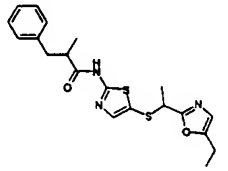
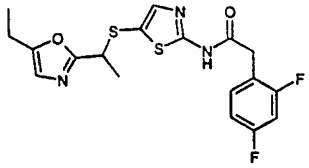
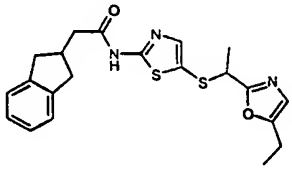
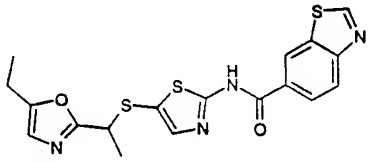
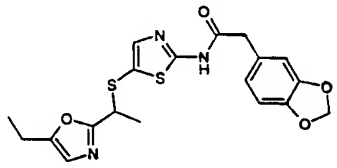
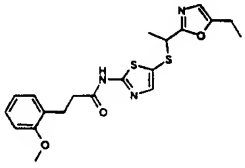
258		C15 H22 N4 O2 S2	355
259		C17 H17 Cl N4 O2 S2	409
260		C18 H20 N4 O2 S2	389
261		C18 H20 N4 O3 S2	405
262		C18 H20 N4 O3 S2	405
263		C18 H20 N4 O3 S2	405
264		C16 H22 N4 O3 S2	341
265		C14 H20 N4 O2 S2	512
266		C17 H27 N5 O2 S2	353
267		C16 H22 N4 O3 S2	425

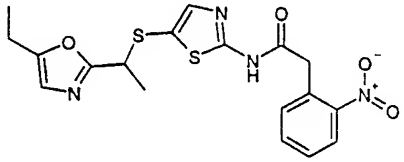
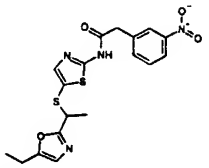
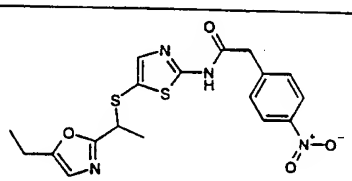
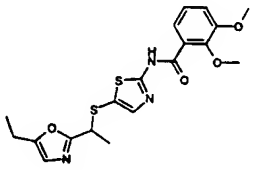
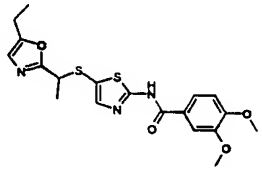
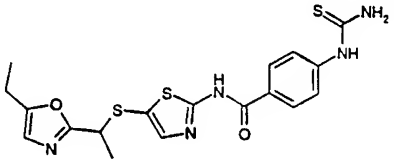
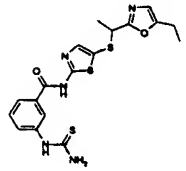
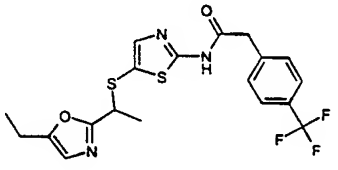
268		C18 H24 N4 O4 S2	401
269		C19 H20 N4 O2 S2	383
270		C17 H26 N4 O2 S2	355
271		C15 H22 N4 O2 S2	433
272		C19 H20 N4 O4 S2	512
273		C16 H21 N5 O3 S2	353
274		C15 H20 N4 O3 S2	367
275		C16 H22 N4 O2 S2	389
276		C16 H21 N5 O3 S2	425
277		C18 H24 N4 O4 S2	369

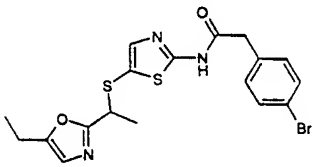
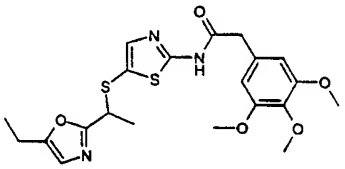
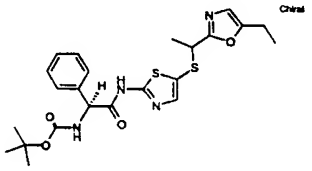
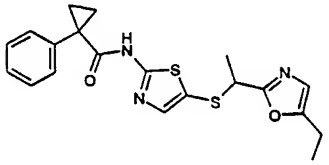
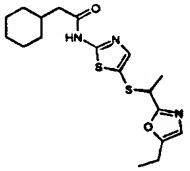
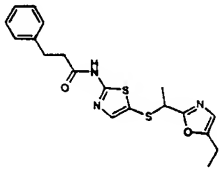
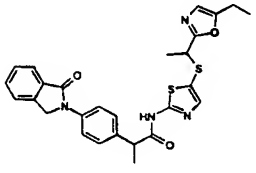
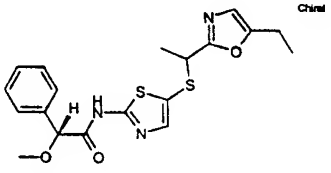
278		C13 H18 N4 O2 S2	465
279		C13 H14 N6 O2 S2	493
280		C15 H18 N6 O2 S2	466
281		C12 H13 N7 O2 S2	366
282		C14 H15 N5 O3 S2	366
283		C13 H14 N6 O2 S3	409
284		C17 H17 Cl N4 O2 S2	387
285		C18 H18 N4 O2 S2	375
286		C17 H18 N4 O2 S2	405

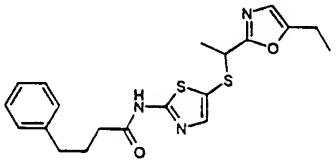
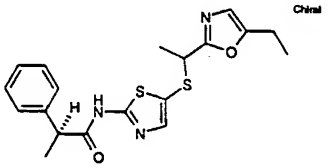
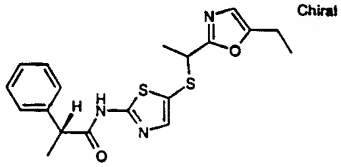
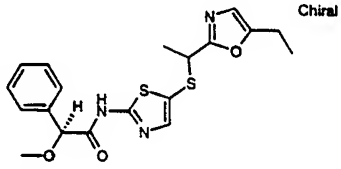
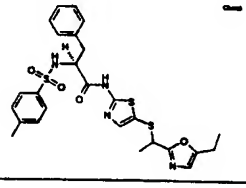
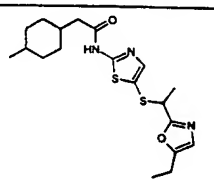
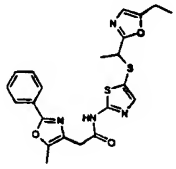
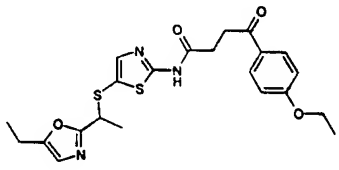
287		C18 H20 N4 O3 S2	389
288		C17 H16 F2 N4 O2 S2	490
289		C16 H17 N5 O2 S2	476
290		C15 H15 N5 O2 S2	510
291		C15 H14 Cl N5 O2 S2	490
292		C16 H17 N5 O2 S2	490
293		C16 H17 N5 O2 S2	476
294		C15 H15 N5 O2 S2	526

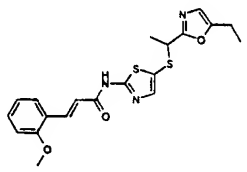
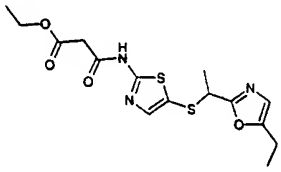
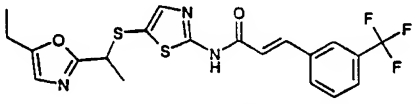
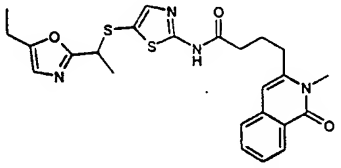
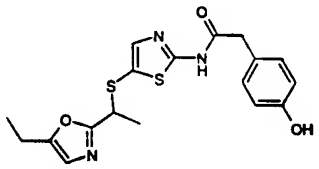
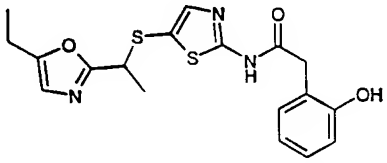
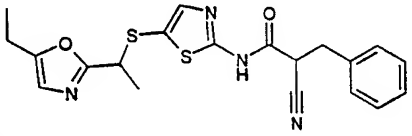
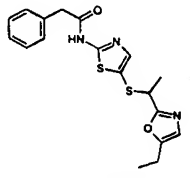
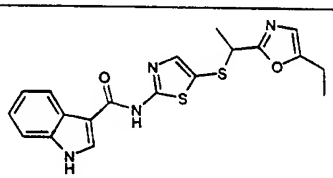
295		C15 H15 N5 O2 S2	540
296		C18 H29 N5 O2 S2	526
297		C14 H19 N3 O2 S2	326
298		C21 H23 N3 O2 S2	414
299		C19 H25 N3 O2 S2	392
300		C22 H21 N3 O2 S2	424
301		C22 H21 N3 O2 S2	424
302		C15 H19 N3 O2 S2	338
303		C16 H23 N3 O2 S2	354

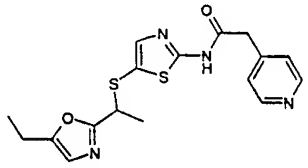
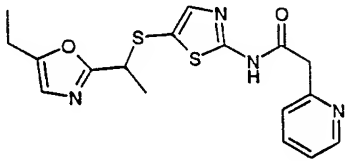
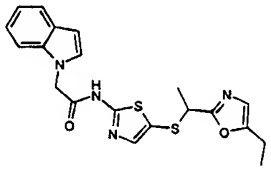
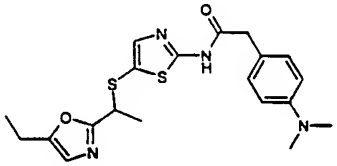
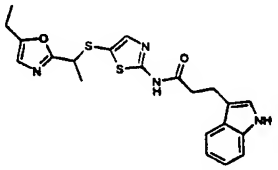
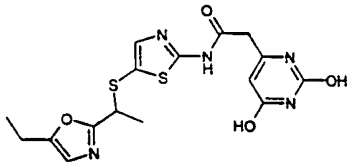
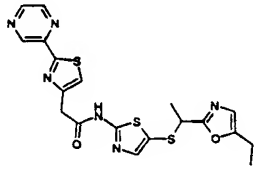
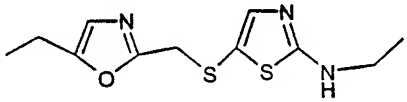
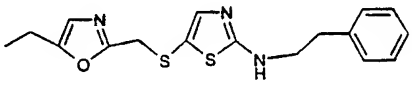
304		C18 H19 N3 O2 S2	374
305		C18 H16 N4 O2 S2	385
306		C20 H23 N3 O2 S2	402
307		C18 H17 F2 N3 O2 S2	410
308		C21 H23 N3 O2 S2	414
309		C18 H16 N4 O2 S3	417
310		C19 H19 N3 O4 S2	418
311		C20 H23 N3 O3 S2	418

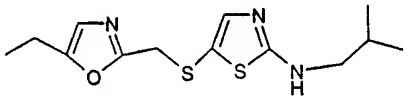
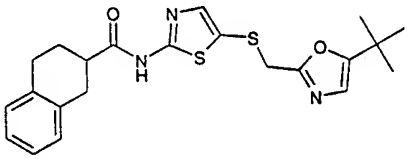
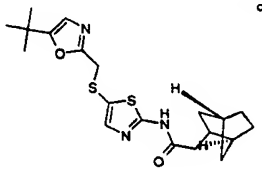
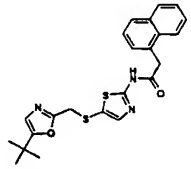
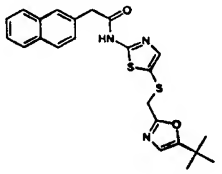
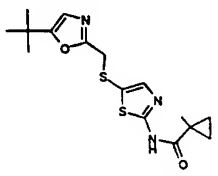
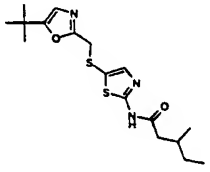
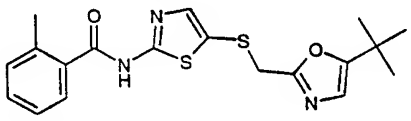
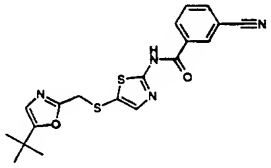
312		C18 H18 N4 O4 S2	419
313		C18 H18 N4 O4 S2	419
314		C18 H18 N4 O4 S2	419
315		C19 H21 N3 O4 S2	420
316		C19 H21 N3 O4 S2	420
317		C18 H19 N5 O2 S3	434
318		C18 H19 N5 O2 S3	434
319		C19 H18 F3 N3 O2 S2	442

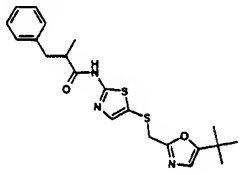
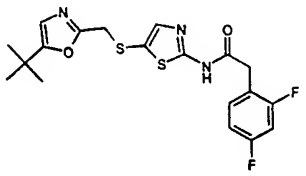
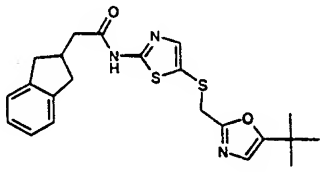
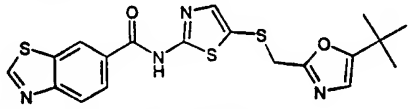
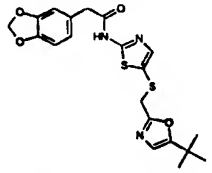
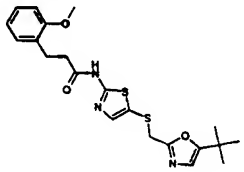
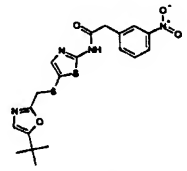
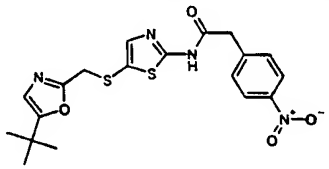
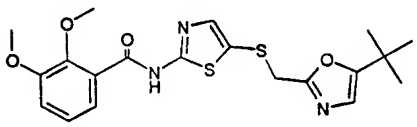
320		C18 H18 Br N3 O2 S2	453
321		C21 H25 N3 O5 S2	464
322		C23 H28 N4 O4 S2	489
323		C20 H21 N3 O2 S2	400
324		C18 H25 N3 O2 S2	380
325		C19 H21 N3 O2 S2	388
326		C27 H26 N4 O3 S2	519
327		C19 H21 N3 O3 S2	404

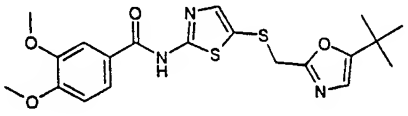
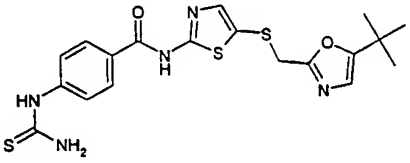
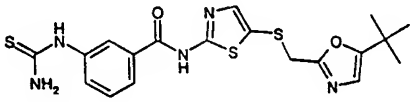
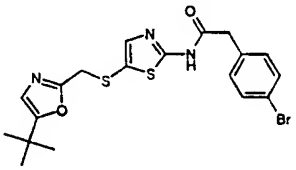
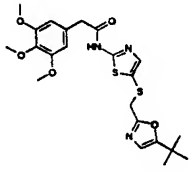
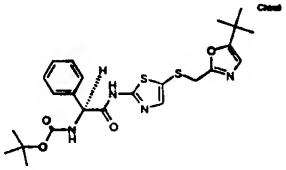
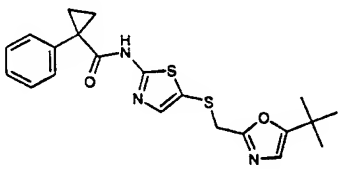
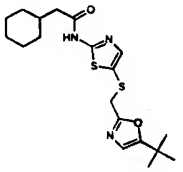
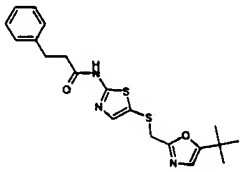
328		C20 H23 N3 O2 S2	402
329		C19 H21 N3 O2 S2	388
330		C19 H21 N3 O2 S2	388
331		C19 H21 N3 O3 S2	404
332		C26 H28 N4 O4 S3	557
333		C19 H27 N3 O2 S2	394
334		C22 H22 N4 O3 S2	455
335		C22 H25 N3 O4 S2	460

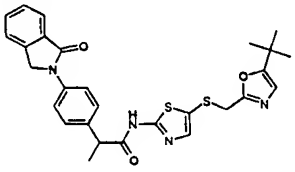
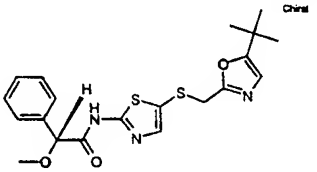
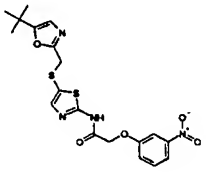
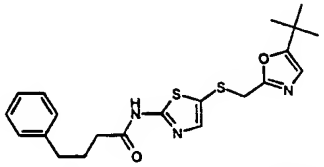
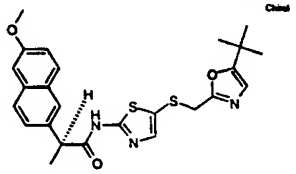
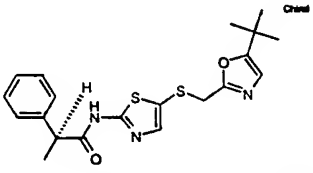
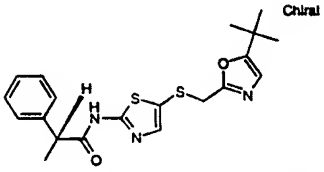
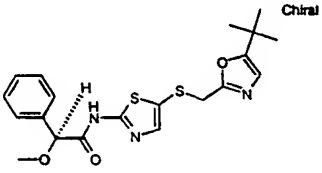
336		C20 H21 N3 O3 S2	416
337		C15 H19 N3 O4 S2	370
338		C20 H18 F3 N3 O2 S2	454
339		C24 H26 N4 O3 S2	483
340		C18 H19 N3 O3 S2	390
341		C18 H19 N3 O3 S2	390
342		C20 H20 N4 O2 S2	413
343		C18 H19 N3 O2 S2	374
344		C19 H18 N4 O2 S2	399

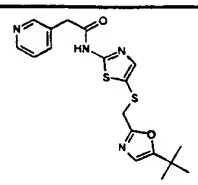
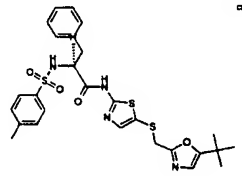
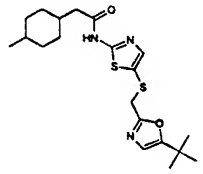
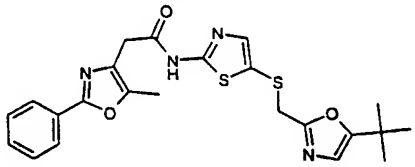
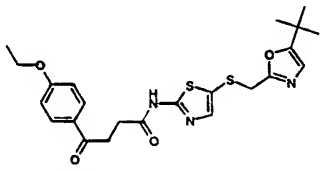
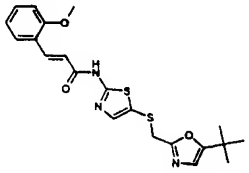
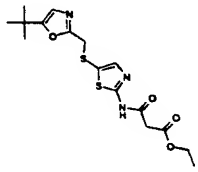
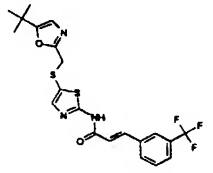
345		C17 H18 N4 O2 S2	489
346		C17 H18 N4 O2 S2	489
347		C20 H20 N4 O2 S2	413
348		C20 H24 N4 O2 S2	531
349		C21 H22 N4 O2 S2	427
350		C16 H17 N5 O4 S2	408
351		C19 H18 N6 O2 S3	687
352		C11 H15 N3 O S2	270
353		C17 H19 N3 O S2	346

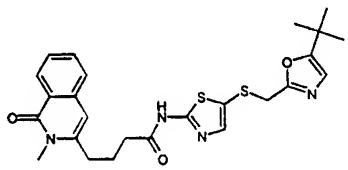
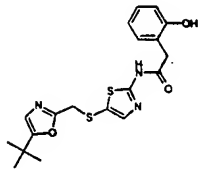
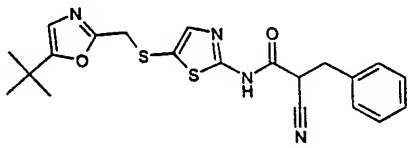
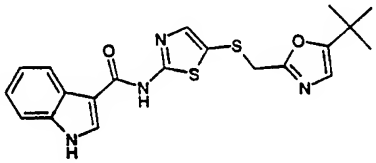
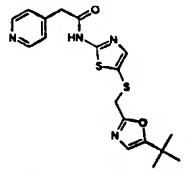
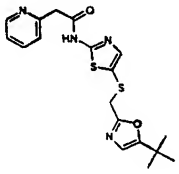
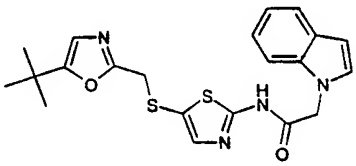
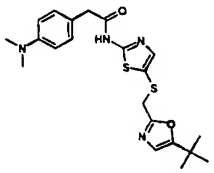
354		C13 H19 N3 O S2	298
355		C22 H25 N3 O2 S2	428
356		C20 H27 N3 O2 S2	406
357		C23 H23 N3 O2 S2	438
358		C23 H23 N3 O2 S2	438
359		C16 H21 N3 O2 S2	352
360		C17 H25 N3 O2 S2	368
361		C19 H21 N3 O2 S2	388
362		C19 H18 N4 O2 S2	399

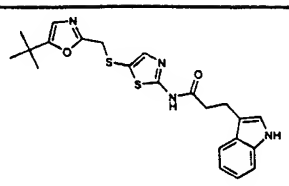
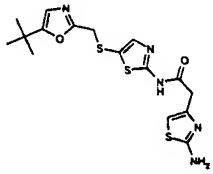
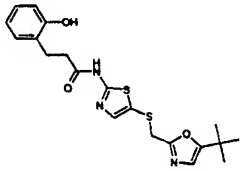
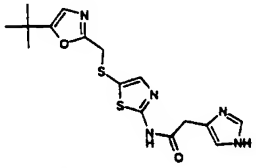
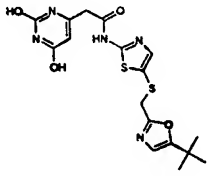
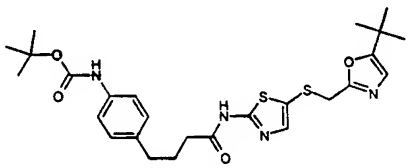
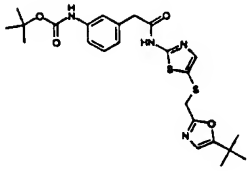
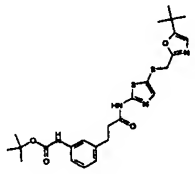
363		C21 H25 N3 O2 S2	416
364		C19 H19 F2 N3 O2 S2	424
365		C22 H25 N3 O2 S2	428
366		C19 H18 N4 O2 S3	431
367		C20 H21 N3 O4 S2	432
368		C21 H25 N3 O3 S2	432
369		C19 H20 N4 O4 S2	433
370		C19 H20 N4 O4 S2	433
371		C20 H23 N3 O4 S2	434

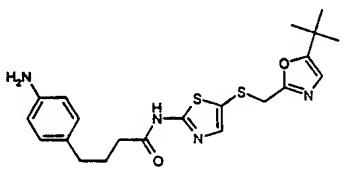
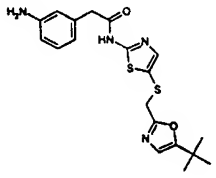
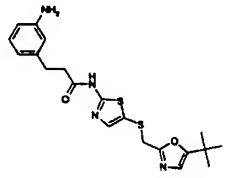
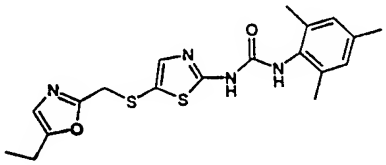
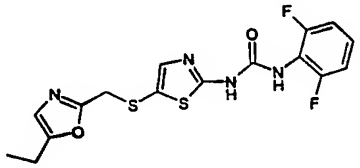
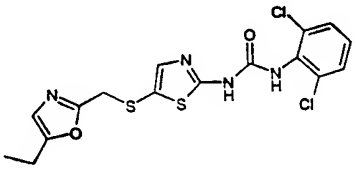
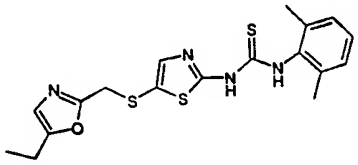
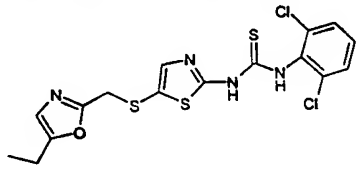
372		C20 H23 N3 O4 S2	434
373		C19 H21 N5 O2 S3	448
374		C19 H21 N5 O2 S3	448
375		C19 H20 Br N3 O2 S2	467
376		C22 H27 N3 O5 S2	478
377		C24 H30 N4 O4 S2	503
378		C21 H23 N3 O2 S2	414
379		C19 H27 N3 O2 S2	394
380		C20 H23 N3 O2 S2	402

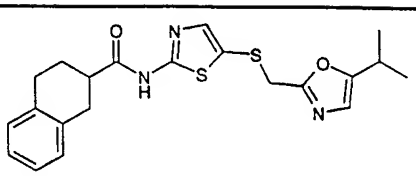
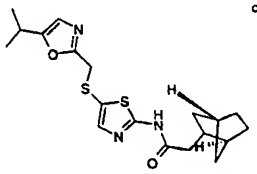
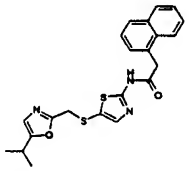
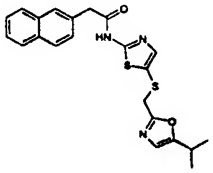
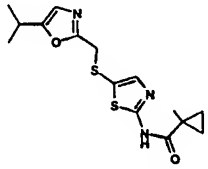
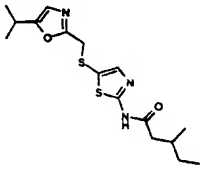
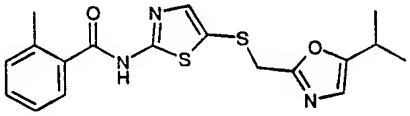
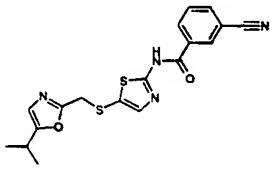
381		C28 H28 N4 O3 S2	533
382		C20 H23 N3 O3 S2	418
383		C19 H20 N4 O5 S2	449
384		C21 H25 N3 O2 S2	416
385		C25 H27 N3 O3 S2	482
386		C20 H23 N3 O2 S2	402
387		C20 H23 N3 O2 S2	402
388		C20 H23 N3 O3 S2	418

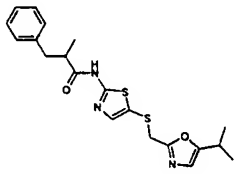
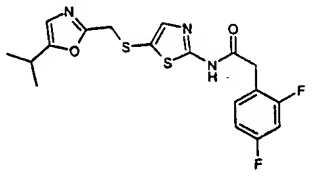
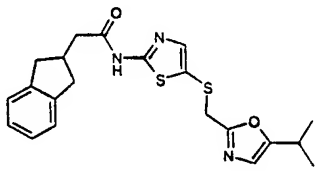
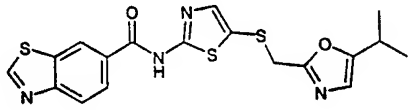
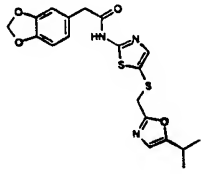
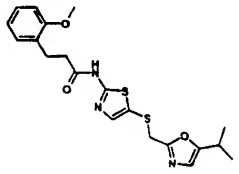
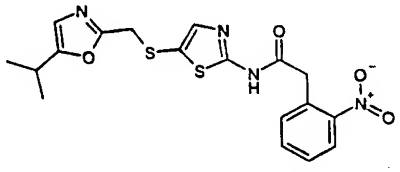
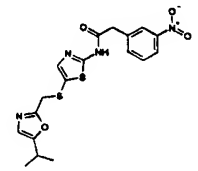
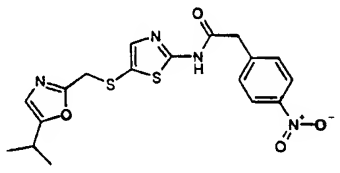
389		C18 H20 N4 O2 S2	503
390		C27 H30 N4 O4 S3	571
391		C20 H29 N3 O2 S2	408
392		C23 H24 N4 O3 S2	469
393		C23 H27 N3 O4 S2	474
394		C21 H23 N3 O3 S2	430
395		C16 H21 N3 O4 S2	384
396		C21 H20 F3 N3 O2 S2	468

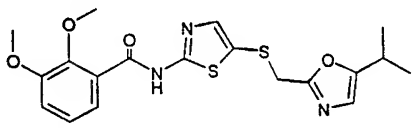
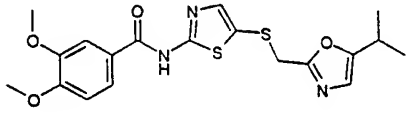
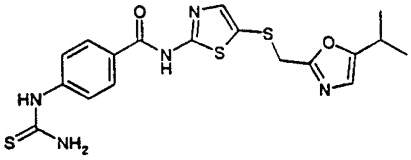
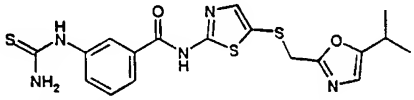
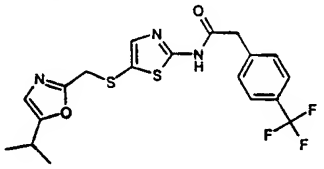
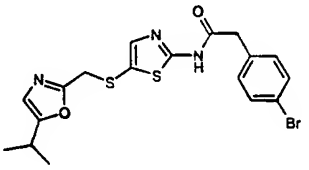
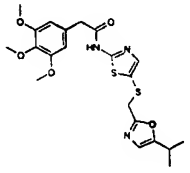
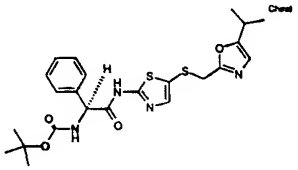
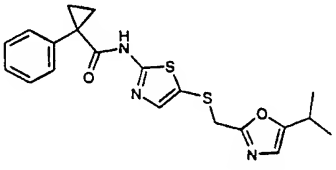
397		C25 H28 N4 O3 S2	497
398		C19 H21 N3 O3 S2	404
399		C21 H22 N4 O2 S2	427
400		C20 H20 N4 O2 S2	413
401		C18 H20 N4 O2 S2	503
402		C18 H20 N4 O2 S2	503
403		C21 H22 N4 O2 S2	427
404		C21 H26 N4 O2 S2	545

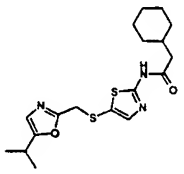
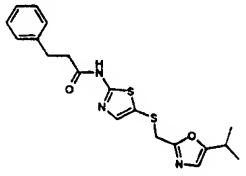
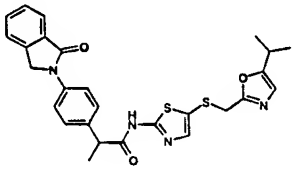
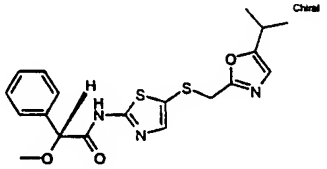
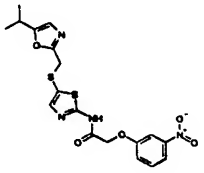
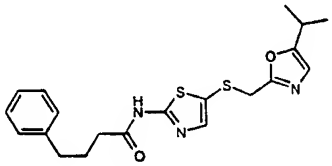
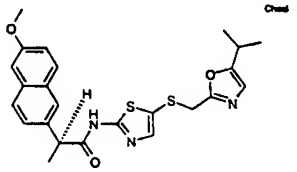
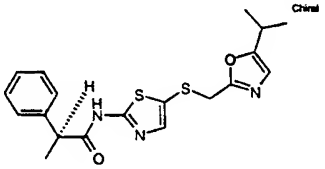
405		C22 H24 N4 O2 S2	441
406		C16 H19 N5 O2 S3	524
407		C20 H23 N3 O3 S2	418
408		C16 H19 N5 O2 S2	492
409		C17 H19 N5 O4 S2	422
410		C26 H34 N4 O4 S2	531
411		C24 H30 N4 O4 S2	503
412		C25 H32 N4 O4 S2	517

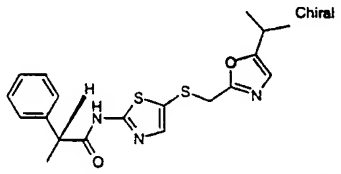
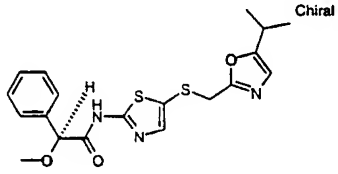
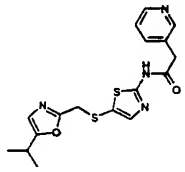
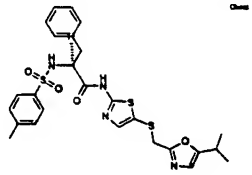
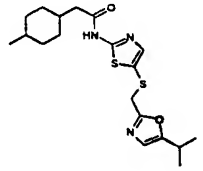
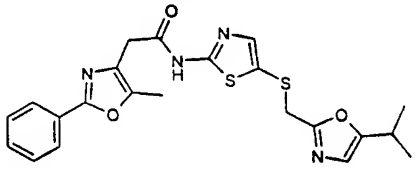
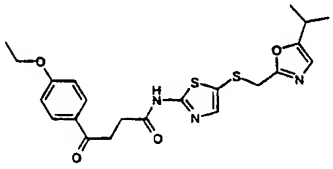
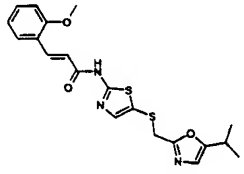
413		C21 H26 N4 O2 S2	545
414		C19 H22 N4 O2 S2	517
415		C20 H24 N4 O2 S2	531
416		C19 H22 N4 O2 S2	403
417		C16 H14 F2 N4 O2 S2	397
418		C16 H14 Cl2 N4 O2 S2	430
419		C18 H20 N4 O S3	405
420		C16 H14 Cl2 N4 O S3	446

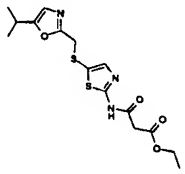
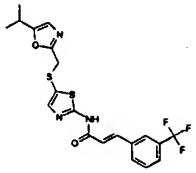
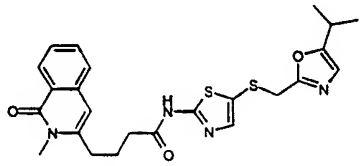
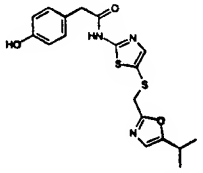
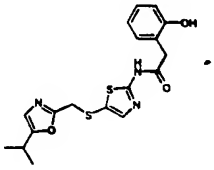
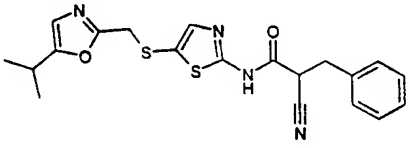
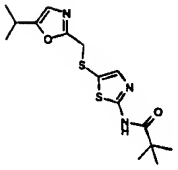
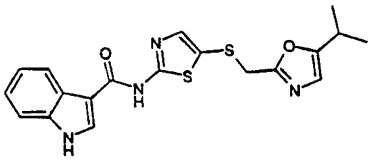
421		C21 H23 N3 O2 S2	414
422		C19 H25 N3 O2 S2	392
423		C22 H21 N3 O2 S2	424
424		C22 H21 N3 O2 S2	424
425		C15 H19 N3 O2 S2	338
426		C16 H23 N3 O2 S2	354
427		C18 H19 N3 O2 S2	374
428		C18 H16 N4 O2 S2	385

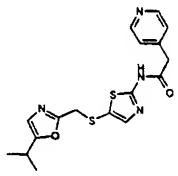
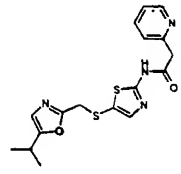
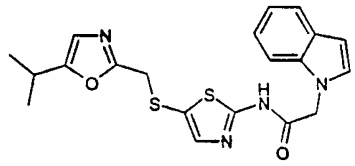
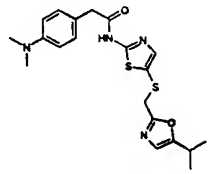
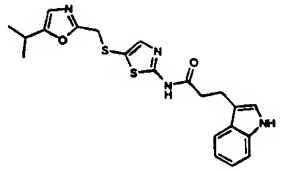
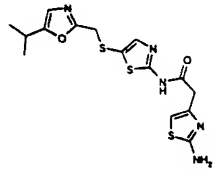
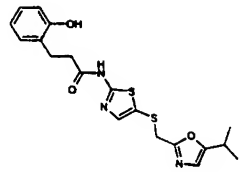
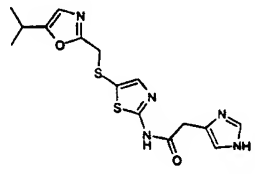
429		C20 H23 N3 O2 S2	402
430		C18 H17 F2 N3 O2 S2	410
431		C21 H23 N3 O2 S2	414
432		C18 H16 N4 O2 S3	417
433		C19 H19 N3 O4 S2	418
434		C20 H23 N3 O3 S2	418
435		C18 H18 N4 O4 S2	419
436		C18 H18 N4 O4 S2	419
437		C18 H18 N4 O4 S2	419

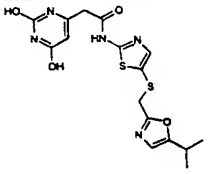
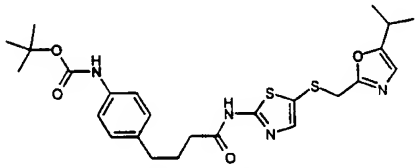
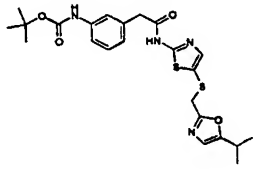
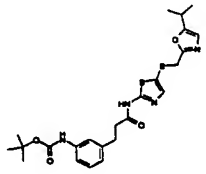
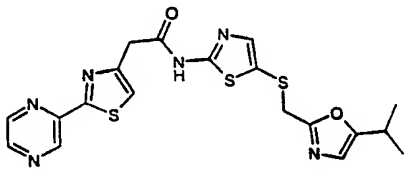
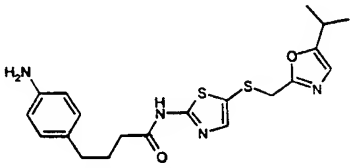
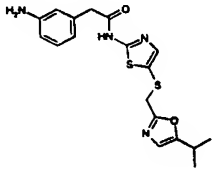
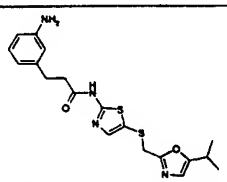
438		C19 H21 N3 O4 S2	420
439		C19 H21 N3 O4 S2	420
440		C18 H19 N5 O2 S3	434
441		C18 H19 N5 O2 S3	434
442		C19 H18 F3 N3 O2 S2	442
443		C18 H18 Br N3 O2 S2	453
444		C21 H25 N3 O5 S2	464
445		C23 H28 N4 O4 S2	489
446		C20 H21 N3 O2 S2	400

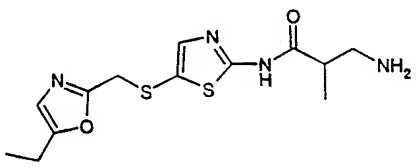
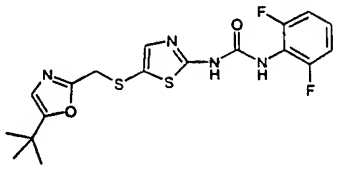
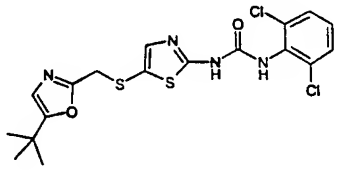
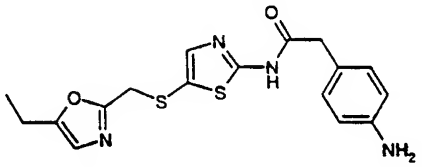
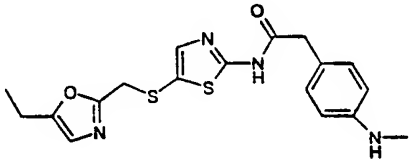
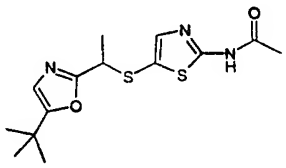
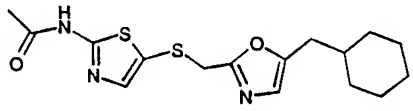
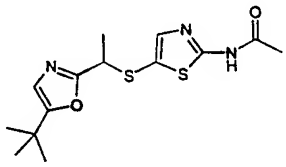
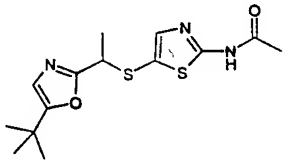
447		C18 H25 N3 O2 S2	380
448		C19 H21 N3 O2 S2	388
449		C27 H26 N4 O3 S2	519
450		C19 H21 N3 O3 S2	404
451		C18 H18 N4 O5 S2	435
452		C20 H23 N3 O2 S2	402
453		C24 H25 N3 O3 S2	468
454		C19 H21 N3 O2 S2	388

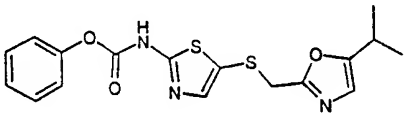
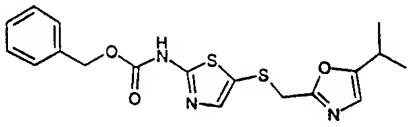
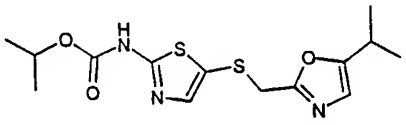
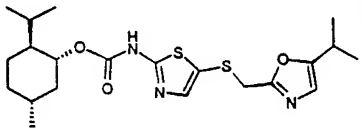
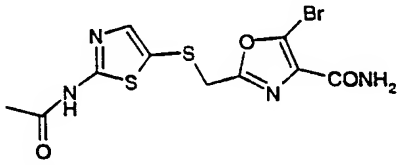
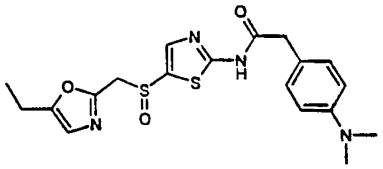
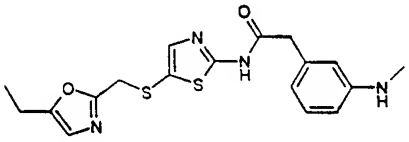
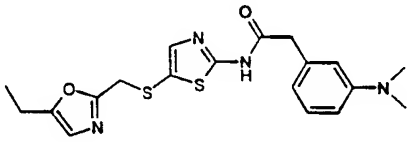
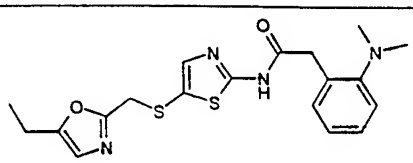
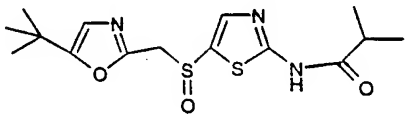
455		C19 H21 N3 O2 S2	388
456		C19 H21 N3 O3 S2	404
457		C17 H18 N4 O2 S2	489
458		C26 H28 N4 O4 S3	557
459		C19 H27 N3 O2 S2	394
460		C22 H22 N4 O3 S2	455
461		C22 H25 N3 O4 S2	460
462		C20 H21 N3 O3 S2	416

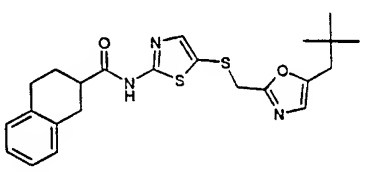
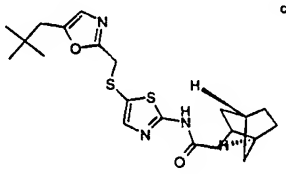
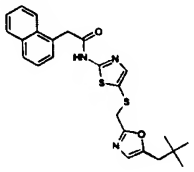
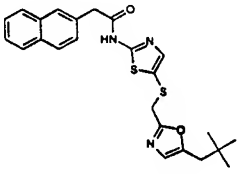
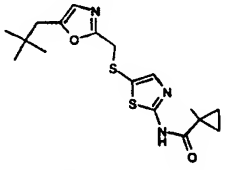
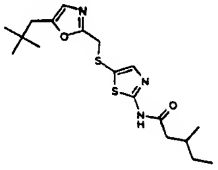
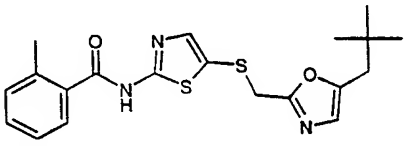
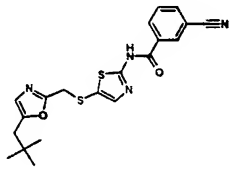
463		C15 H19 N3 O4 S2	370
464		C20 H18 F3 N3 O2 S2	454
465		C24 H26 N4 O3 S2	483
466		C18 H19 N3 O3 S2	390
467		C18 H19 N3 O3 S2	390
468		C20 H20 N4 O2 S2	413
469		C15 H21 N3 O2 S2	340
470		C19 H18 N4 O2 S2	399

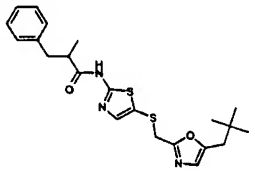
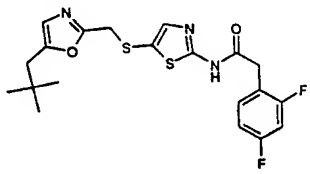
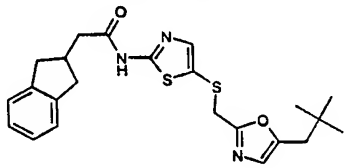
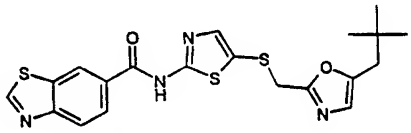
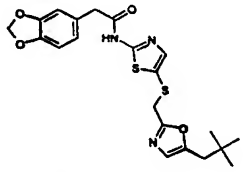
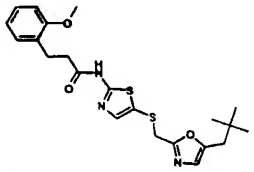
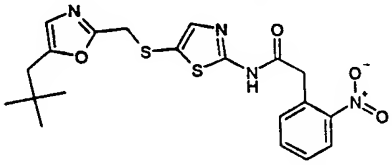
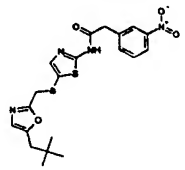
471		C17 H18 N4 O2 S2	489
472		C17 H18 N4 O2 S2	489
473		C20 H20 N4 O2 S2	413
474		C20 H24 N4 O2 S2	531
475		C21 H22 N4 O2 S2	427
476		C15 H17 N5 O2 S3	510
477		C19 H21 N3 O3 S2	404
478		C15 H17 N5 O2 S2	478

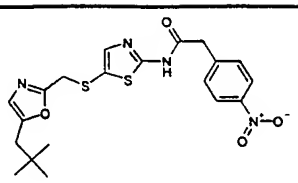
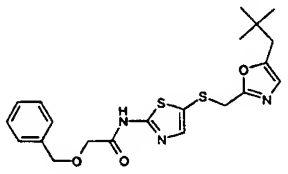
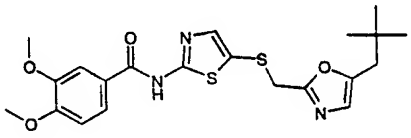
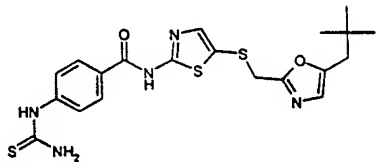
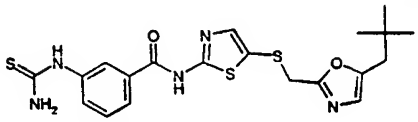
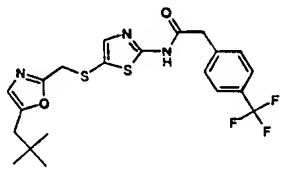
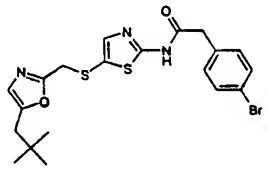
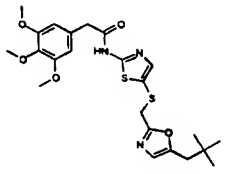
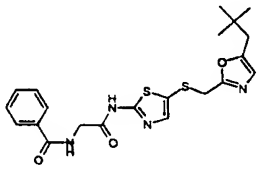
479		C16 H17 N5 O4 S2	408
480		C25 H32 N4 O4 S2	517
481		C23 H28 N4 O4 S2	489
482		C24 H30 N4 O4 S2	503
483		C19 H18 N6 O2 S3	459
484		C20 H24 N4 O2 S2	531
485		C18 H20 N4 O2 S2	503
486		C19 H22 N4 O2 S2	517

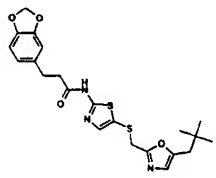
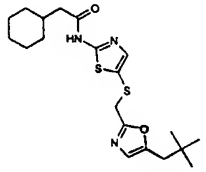
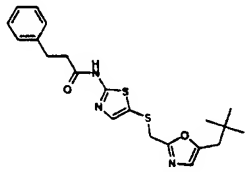
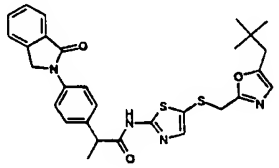
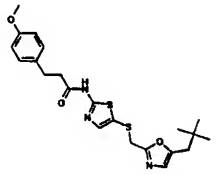
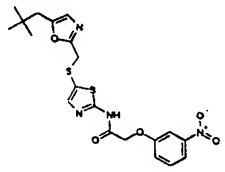
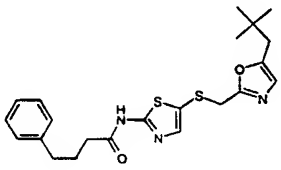
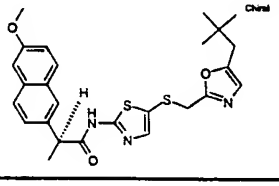
487		C13 H18 N4 O2 S2	363
488		C18 H18 F2 N4 O2 S2	425
489		C18 H18 Cl2 N4 O2 S2	458
490		C17 H18 N4 O2 S2	489
491		C18 H20 N4 O2 S2	389
492		C14 H19 N3 O2 S2	326
493		C16 H21 N3 O2 S2	352
494		C14 H19 N3 O2 S2	326
495		C14 H19 N3 O2 S2	326

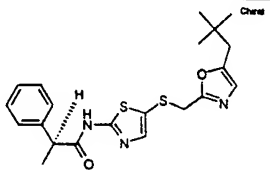
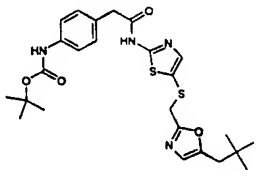
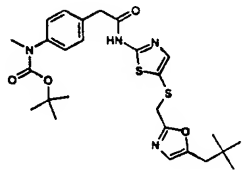
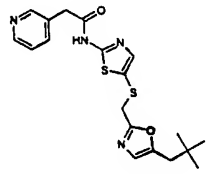
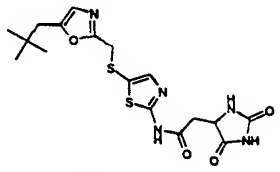
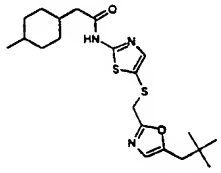
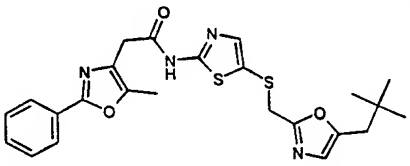
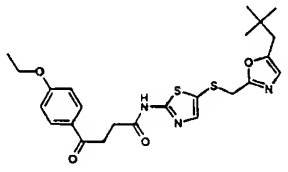
496		C17 H17 N3 O3 S2	**376**
497		C18 H19 N3 O3 S2	**390**
498		C14 H19 N3 O3 S2	**342**
499	 Chiral	C21 H31 N3 O3 S2	**438**
500		C10 H9 Br N4 O3 S2	**378**
501		C19 H22 N4 O3 S2	**419**
502		C18 H20 N4 O2 S2	**389**
503		C19 H22 N4 O2 S2	**403**
504		C19 H22 N4 O2 S2	**403**
505		C15 H21 N3 O3 S2	**356**

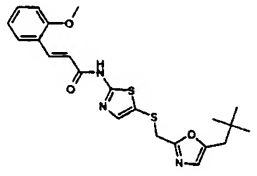
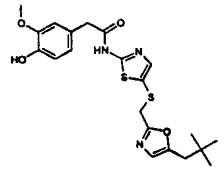
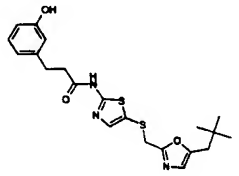
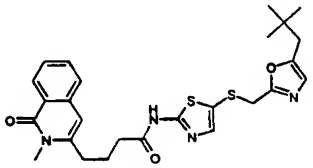
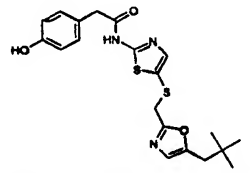
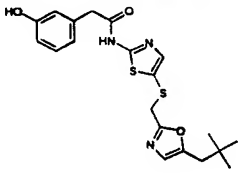
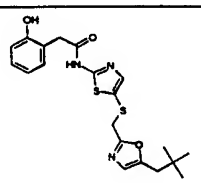
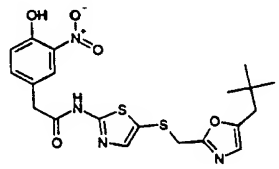
506		C23 H27 N3 O2 S2	442
507		C21 H29 N3 O2 S2	420
508		C24 H25 N3 O2 S2	452
509		C24 H25 N3 O2 S2	452
510		C17 H23 N3 O2 S2	366
511		C18 H27 N3 O2 S2	382
512		C20 H23 N3 O2 S2	402
513		C20 H20 N4 O2 S2	413

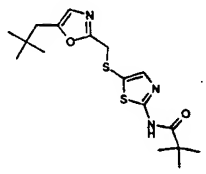
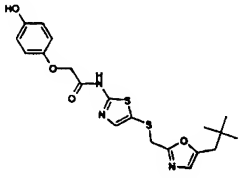
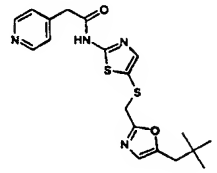
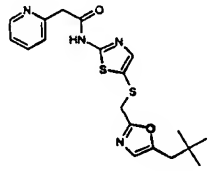
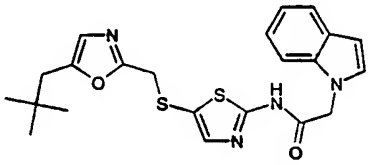
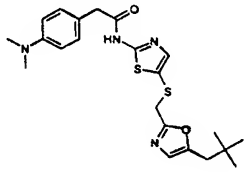
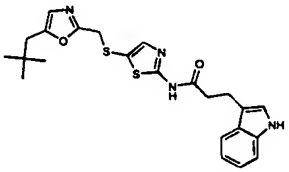
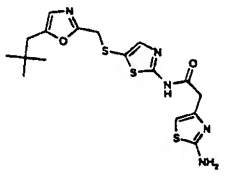
514		C22 H27 N3 O2 S2	430
515		C20 H21 F2 N3 O2 S2	438
516		C23 H27 N3 O2 S2	442
517		C20 H20 N4 O2 S3	445
518		C21 H23 N3 O4 S2	446
519		C22 H27 N3 O3 S2	446
520		C20 H22 N4 O4 S2	447
521		C20 H22 N4 O4 S2	447

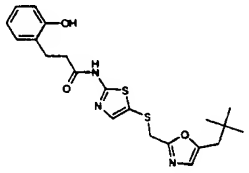
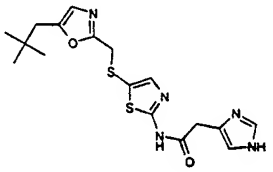
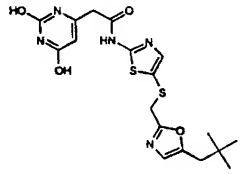
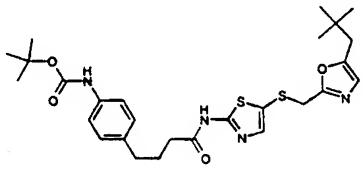
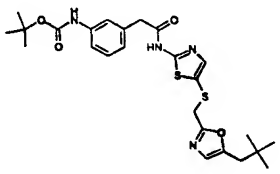
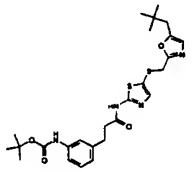
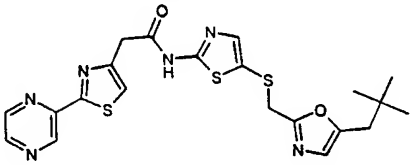
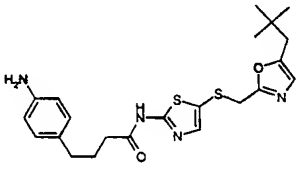
522		C20 H22 N4 O4 S2	447
523		C21 H25 N3 O3 S2	432
524		C21 H25 N3 O4 S2	448
525		C20 H23 N5 O2 S3	462
526		C20 H23 N5 O2 S3	462
527		C21 H22 F3 N3 O2 S2	470
528		C20 H22 Br N3 O2 S2	481
529		C23 H29 N3 O5 S2	492
530		C21 H24 N4 O3 S2	445

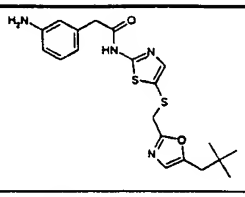
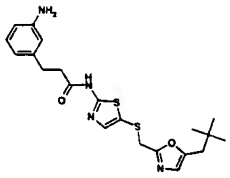
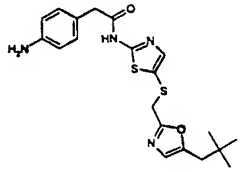
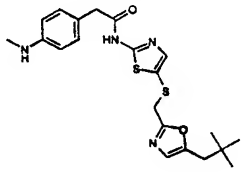
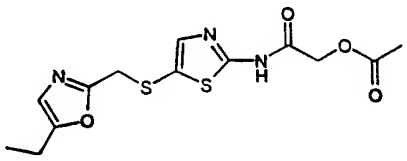
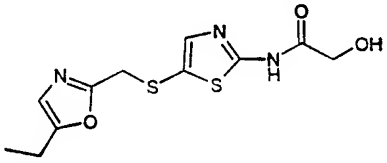
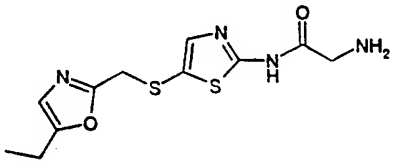
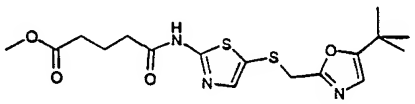
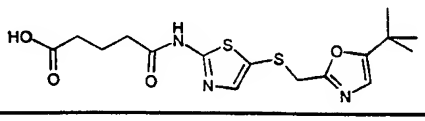
531		C22 H25 N3 O4 S2	460
532		C20 H29 N3 O2 S2	408
533		C21 H25 N3 O2 S2	416
534		C29 H30 N4 O3 S2	547
535		C22 H27 N3 O3 S2	446
536		C20 H22 N4 O5 S2	463
537		C22 H27 N3 O2 S2	430
538		C26 H29 N3 O3 S2	496

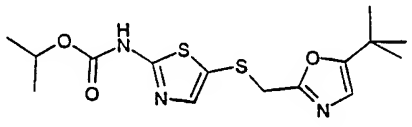
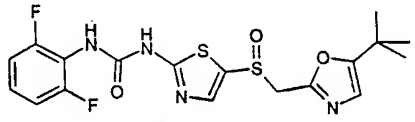
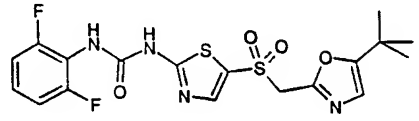
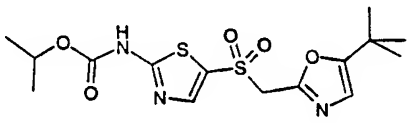
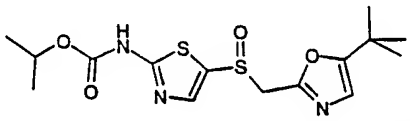
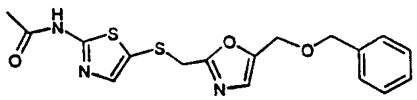
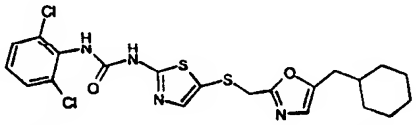
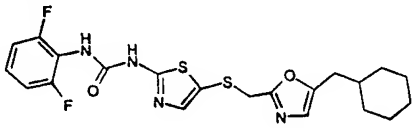
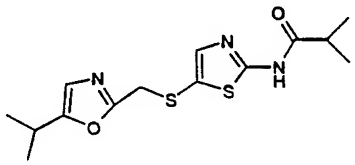
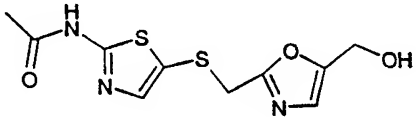
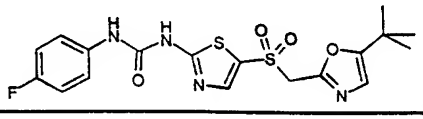
539		C21 H25 N3 O2 S2	416
540		C25 H32 N4 O4 S2	517
541		C26 H34 N4 O4 S2	531
542		C19 H22 N4 O2 S2	517
543		C17 H21 N5 O4 S2	424
544		C21 H31 N3 O2 S2	422
545		C24 H26 N4 O3 S2	483
546		C24 H29 N3 O4 S2	488

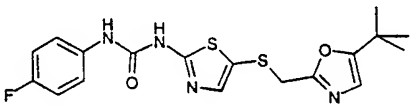
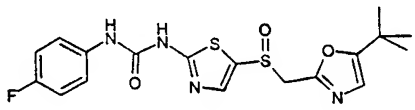
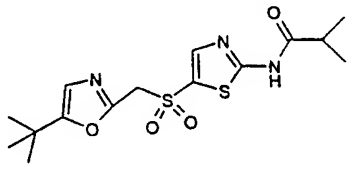
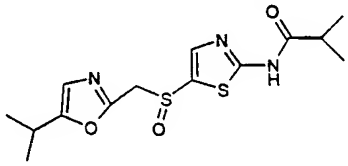
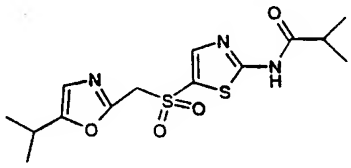
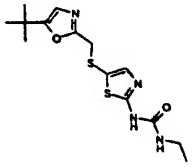
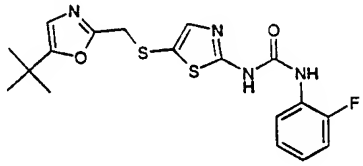
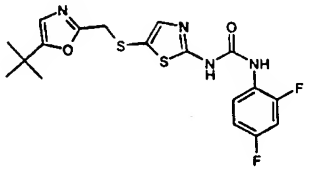
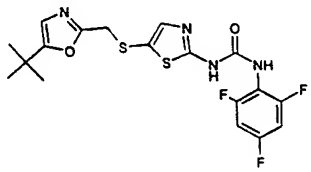
547		C22 H25 N3 O3 S2	444
548		C21 H25 N3 O4 S2	448
549		C21 H25 N3 O3 S2	432
550		C26 H30 N4 O3 S2	511
551		C20 H23 N3 O3 S2	418
552		C20 H23 N3 O3 S2	418
553		C20 H23 N3 O3 S2	418
554		C20 H22 N4 O5 S2	463

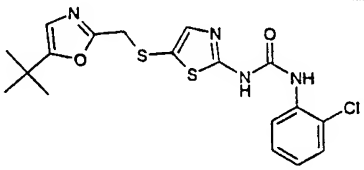
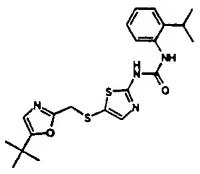
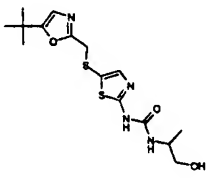
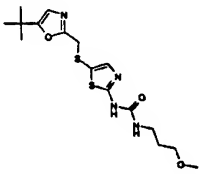
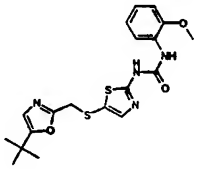
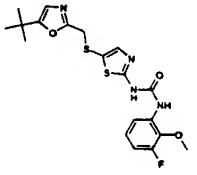
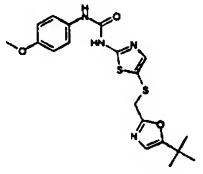
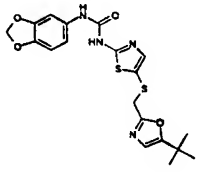
555		C17 H25 N3 O2 S2	368
556		C20 H23 N3 O4 S2	434
557		C19 H22 N4 O2 S2	517
558		C19 H22 N4 O2 S2	517
559		C22 H24 N4 O2 S2	441
560		C22 H28 N4 O2 S2	559
561		C23 H26 N4 O2 S2	569
562		C17 H21 N5 O2 S3	538

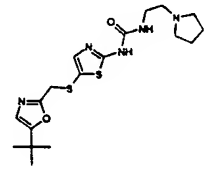
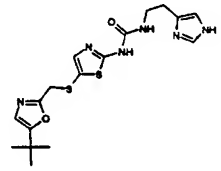
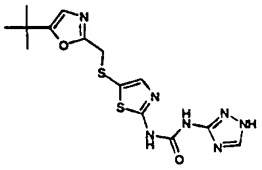
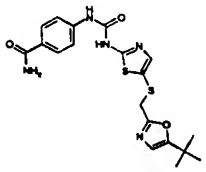
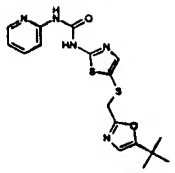
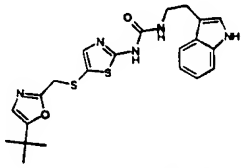
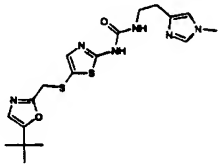
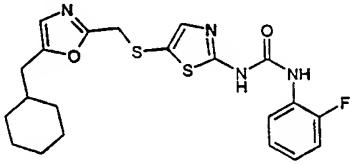
563		C21 H25 N3 O3 S2	432
564		C17 H21 N5 O2 S2	506
565		C18 H21 N5 O4 S2	436
566		C27 H36 N4 O4 S2	545
567		C25 H32 N4 O4 S2	517
568		C26 H34 N4 O4 S2	531
569		C21 H22 N6 O2 S3	487
570		C22 H28 N4 O2 S2	559

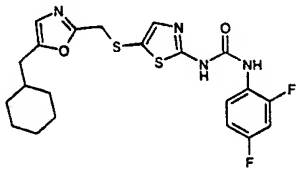
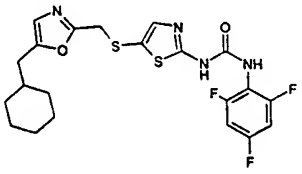
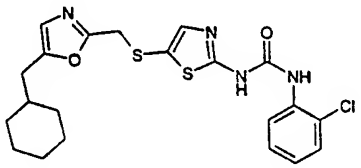
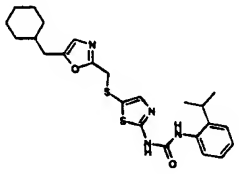
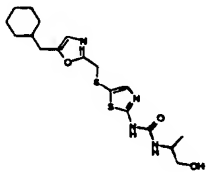
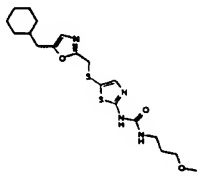
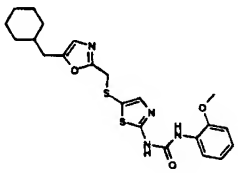
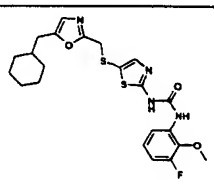
571		C20 H24 N4 O2 S2	531
572		C21 H26 N4 O2 S2	545
573		C20 H24 N4 O2 S2	531
574		C21 H26 N4 O2 S2	545
575		C13 H15 N3 O4 S2	342
576		C11 H13 N3 O3 S2	300
577		C11 H14 N4 O2 S2	413
578		C17 H23 N3 O4 S2	398
579		C16 H21 N3 O4 S2	384

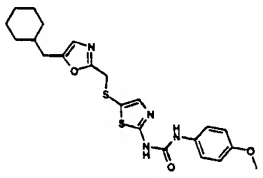
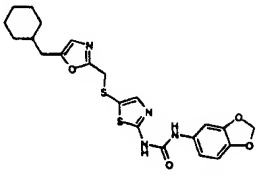
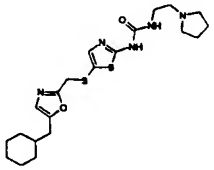
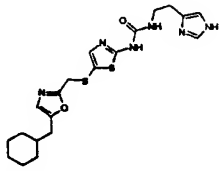
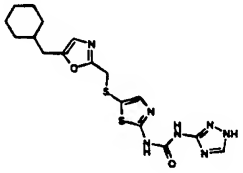
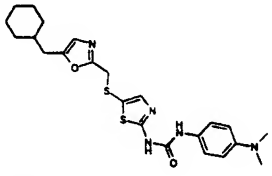
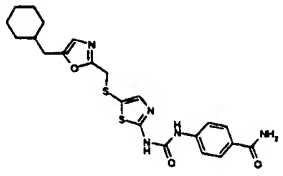
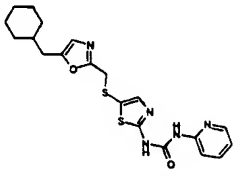
580		C15 H21 N3 O3 S2	356
581		C18 H18 F2 N4 O3 S2	441
582		C18 H18 F2 N4 O4 S2	457
583		C15 H21 N3 O5 S2	388
584		C15 H21 N3 O4 S2	372
585		C17 H17 N3 O3 S2	376
586		C21 H22 Cl2 N4 O2 S2	498
587		C21 H22 F2 N4 O2 S2	465
588		C14 H19 N3 O2 S2	326
589		C10 H11 N3 O3 S2	286
590		C18 H19 F N4 O4 S2	439

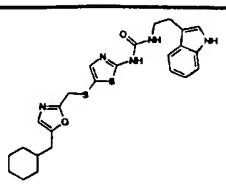
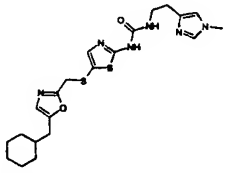
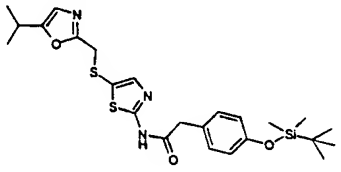
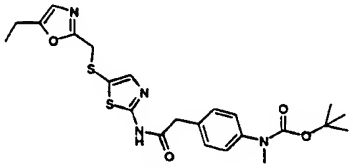
591		C18 H19 F N4 O2 S2	407
592		C18 H19 F N4 O3 S2	423
593		C15 H21 N3 O4 S2	372
594		C14 H19 N3 O3 S2	342
595		C14 H19 N3 O4 S2	358
596		C14 H20 N4 O2 S2	341
597		C18 H19 F N4 O2 S2	407
598		C18 H18 F2 N4 O2 S2	425
599		C18 H17 F3 N4 O2 S2	443

600		C18 H19 Cl N4 O2 S2	**423**
601		C21 H26 N4 O2 S2	**431**
602		C15 H22 N4 O3 S2	**371**
603		C16 H24 N4 O3 S2	**385**
604		C19 H22 N4 O3 S2	**419**
605		C19 H21 F N4 O3 S2	**437**
606		C19 H22 N4 O3 S2	**419**
607		C19 H20 N4 O4 S2	**433**

608		C18 H27 N5 O2 S2	524
609		C17 H22 N6 O2 S2	521
610		C14 H17 N7 O2 S2	494
611		C19 H21 N5 O3 S2	432
612		C17 H19 N5 O2 S2	504
613		C22 H25 N5 O2 S2	456
614		C18 H24 N6 O2 S2	535
615		C21 H23 F N4 O2 S2	447

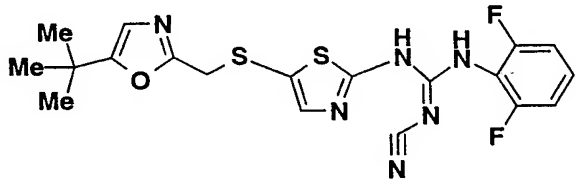
616		C21 H22 F2 N4 O2 S2	465
617		C21 H21 F3 N4 O2 S2	483
618		C21 H23 Cl N4 O2 S2	464
619		C24 H30 N4 O2 S2	471
620		C18 H26 N4 O3 S2	411
621		C19 H28 N4 O3 S2	425
622		C22 H26 N4 O3 S2	459
623		C22 H25 F N4 O3 S2	477

624		C22 H26 N4 O3 S2	459
625		C22 H24 N4 O4 S2	473
626		C21 H31 N5 O2 S2	564
627		C20 H26 N6 O2 S2	561
628		C17 H21 N7 O2 S2	534
629		C23 H29 N5 O2 S2	586
630		C22 H25 N5 O3 S2	472
631		C20 H23 N5 O2 S2	544

632		C25 H29 N5 O2 S2	496
633		C21 H28 N6 O2 S2	575
634		C24 H33 N3 O3 S2 Si	504
635		C23 H28 N4 O4 S2	489

Example 636

Preparation of N-[5-[[(5-*t*-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-N'-cyano-N"-(2,6-difluorophenyl)guanidine.



A solution of 100 mg of N-[5-[[(5-*t*-Butyl-2-oxazolyl)methyl]thio]-2-aminothiazole and 68 mg of 2,6-difluorophenyl isothiocyanate was heated at 65°C for 16 hours under argon. The solution was evaporated to dryness and the residue purified by flash chromatography to give 91 mg of the intermediate thiourea.

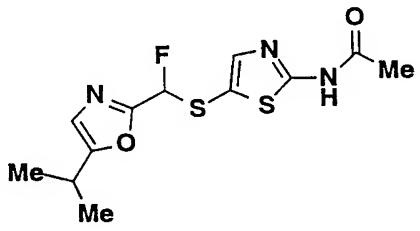
To a solution of 30 mg of N-[5-[[(5-*t*-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]-N"-(2,6-difluorophenyl)thiourea, 52 mg of ethyl-3(3-dimethylamino)propyl carbodiimide hydrochloride and 48 μL of diisopropylethylamine in 0.5 mL methylene chloride was added a solution of 29 mg of cyanamide in 0.1 mL tetrahydrofuran. After stirring for 1 hr, the solvent was removed and the crude material purified by HPLC to give 8 mg of Example 636 compound.

MS: $(M+H)^+$ 449^+

^1H NMR (400 MHz, $CDCl_3$): d 1.27 (9H, s), 4.19 (2H, s), 6.69 (1H, s), 7.03 (2H, m), 7.35 (1H, m), 8.74 (1H, s).

Example 637

Preparation of N-[5-[[(5-isopropyl-2-oxazolyl)fluoromethyl]thio]-2-thiazolyl acetamide.



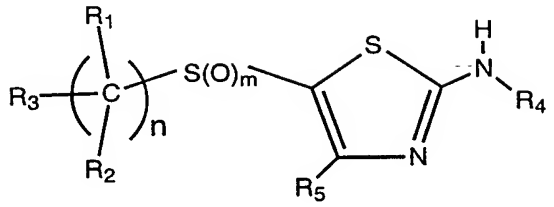
To a stirred mixture of 2-acetamido-5-thiazole thiol acetate (141 mg) in 3 mL of dry THF under argon was added 1N t-BuOK in THF (0.72 mL). This mixture was stirred at room temperature for 25 min, and a solution of 5-isopropyl-(2-(chlorofluoromethyl))oxazole (116 mg) in 2 mL of dry THF was added. The reaction mixture was stirred at 60°C for 18 hr, diluted with 150 mL of EtOAc and washed with saturated NH_4Cl solution (2x25 mL), saturated $NaHCO_3$ solution (1x25 mL) and brine (1x25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give Example 637 compound.

MS: (M+H)+ 316

HPLC retention time 3.52 min. (Column: YMC ODS S05 4.6 X 50 mm column, 0% to 100% B gradient in 4 min. Solvent A: 10% CH_3OH/90% H_2O/0.2% H_3PO_4; Solvent B: 90% CH_3OH/10% H_2O/0.2% H_3PO_4; UV: 220 nM).

What is Claimed is:

1. A compound of the formula



(I)

and pharmaceutically acceptable salts thereof wherein:

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is aryl or heteroaryl;

R_4 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

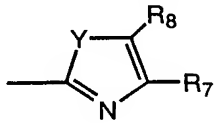
SO_2-alkyl, SO_2-cycloalkyl, SO_2-aryl, SO_2-alkyl-cycloalkyl, SO_2-alkyl-aryl, SO_2-heteroaryl, SO_2-alkyl-heteroaryl, SO_2-heterocycloalkyl, SO_2-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

$C(NNO_2)NH$-alkyl, $C(NNO_2)NH$-cycloalkyl, $C(NNO_2)NH$-aryl,

$C(NNO_2)NH$-alkyl-cycloalkyl, $C(NNO_2)NH$-alkyl-aryl,
$C(NNO_2)NH$-heteroaryl, $C(NNO_2)NH$-alkyl-heteroaryl,
$C(NNO_2)NH$-heterocyloalkyl, $C(NNO_2)NH$-alkyl-heterocycloalkyl;
or
C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl,
C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl,
C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl,
C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or
C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl,
C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl,
C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl,
C(NH)NHCO-heterocylcloalkyl,
C(NH)NHCO-alkyl-heterocycloalkyl; or
$C(NOR_6)NH$-alkyl, $C(NOR_6)NH$-cycloalkyl, $C(NOR_6)NH$-aryl,
$C(NOR_6)NH$-alkyl-cycloalkyl, $C(NOR_6)NH$-alkyl-aryl,
$C(NOR_6)NH$-heteroaryl, $C(NOR_6)NH$-alkyl-heteroaryl,
$C(NOR_6)NH$-heterocylcoalkyl, $C(NOR_6)NH$-alkyl-heterocycloalkyl;
R_5 is hydrogen or alkyl;
R_6 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl,
heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;
m is an integer of 0 to 2; and
n is an integer of 1 to 3.

2. The compounds as recited in Claim 1, wherein
R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is oxygen, sulfur or NR_9
R_4 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl,
heteroaryl, heteroarylalkyl, heterocycloalkyl,
heterocycloalkylalkyl; or
CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl,

CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

SO_2-alkyl, SO_2-cycloalkyl, SO_2-aryl, SO_2-alkyl-cycloalkyl, SO_2-alkyl-aryl, SO_2-heteroaryl, SO_2-alkyl-heteroaryl, SO_2-heterocycloalkyl, SO_2-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

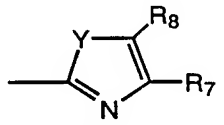
$C(NNO_2)NH$-alkyl, $C(NNO_2)NH$-cycloalkyl, $C(NNO_2)NH$-aryl, $C(NNO_2)NH$-alkyl-cycloalkyl, $C(NNO_2)NH$-alkyl-aryl, $C(NNO_2)NH$-heteroaryl, $C(NNO_2)NH$-alkyl-heteroaryl, $C(NNO_2)NH$-heterocyloalkyl, $C(NNO_2)NH$-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

$C(NOR_6)NH$-alkyl, $C(NOR_6)NH$-cycloalkyl, $C(NOR_6)NH$-aryl, $C(NOR_6)NH$-alkyl-cycloalkyl, $C(NOR_6)NH$-alkyl-aryl,

$C(NOR_6)NH$-heteroaryl, $C(NOR_6)NH$-alkyl-heteroaryl,
$C(NOR_6)NH$-heterocylcoalkyl, $C(NOR_6)NH$-alkyl-heterocycloalkyl;
R_5 is hydrogen or alkyl;
R_6 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;
R_7 and R_8 are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, subsituted aryl, cycloalkylalkyl, arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;
R_9 is hydrogen, alkyl, cycloalkyl, aryl, akylcycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;
m is an integer of 0 to 2; and
n is an integer of 1 to 3.

3. The compounds as recited in Claim 1, wherein
R_1 and R_2 are independently hydrogen, fluorine or alkyl;
R_3 is 

wherein Y is oxygen;
R_4 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl,
heterocycloalkylalkyl; or
CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or
CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl,
CONH-alkyl-heteroaryl, CONH-heterocycloalkyl,
CONH-alkyl-heterocycloalkyl; or
COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

SO_2-alkyl, SO_2-cycloalkyl, SO_2-aryl, SO_2-alkyl-cycloalkyl, SO_2-alkyl-aryl, SO_2-heteroaryl, SO_2-alkyl-heteroaryl, SO_2-heterocycloalkyl, SO_2-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

C(NNO_2)NH-alkyl, C(NNO_2)NH-cycloalkyl, C(NNO_2)NH-aryl, C(NNO_2)NH-alkyl-cycloalkyl, C(NNO_2)NH-alkyl-aryl, C(NNO_2)NH-heteroaryl, C(NNO_2)NH-alkyl-heteroaryl, C(NNO_2)NH-heterocyloalkyl, C(NNO_2)NH-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

C(NOR_6)NH-alkyl, C(NOR_6)NH-cycloalkyl, C(NOR_6)NH-aryl, C(NOR_6)NH-alkyl-cycloalkyl, C(NOR_6)NH-alkyl-aryl, C(NOR_6)NH-heteroaryl, C(NOR_6)NH-alkyl-heteroaryl, C(NOR_6)NH-heterocylcoalkyl, C(NOR_6)NH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_6 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

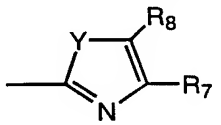
R_7 and R_8 are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, subsituted aryl, cycloalkylalkyl, arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

4. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is sulfur;

R_4 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl,
heterocycloalkylalkyl; or
CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl,
CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl,
CO-alkyl-heterocycloalkyl; or
CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl,
CONH-alkyl-aryl, CONH-heteroaryl,
CONH-alkyl-heteroaryl, CONH-heterocycloalkyl,
CONH-alkyl-heterocycloalkyl; or
COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl,
COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl,
COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or
SO_2-alkyl, SO_2-cycloalkyl, SO_2-aryl, SO_2-alkyl-cycloalkyl, SO_2-alkyl-aryl,
SO_2-heteroaryl, SO_2-alkyl-heteroaryl, SO_2-heterocycloalkyl,
SO_2-alkyl-heterocycloalkyl; or
C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl,
C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl,
C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl,
C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl;
or
$C(NNO_2)NH$-alkyl, $C(NNO_2)NH$-cycloalkyl, $C(NNO_2)NH$-aryl,
$C(NNO_2)NH$-alkyl-cycloalkyl, $C(NNO_2)NH$-alkyl-aryl,
$C(NNO_2)NH$-heteroaryl, $C(NNO_2)NH$-alkyl-heteroaryl,

$C(NNO_2)$NH-heterocyloalkyl, $C(NNO_2)$NH-alkyl-heterocycloalkyl;

or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl,
C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl,
C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl,
C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl,
C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl,
C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl,
C(NH)NHCO-heterocylcloalkyl,
C(NH)NHCO-alkyl-heterocycloalkyl; or

$C(NOR_6)$NH-alkyl, $C(NOR_6)$NH-cycloalkyl, $C(NOR_6)$NH-aryl,
$C(NOR_6)$NH-alkyl-cycloalkyl, $C(NOR_6)$NH-alkyl-aryl,
$C(NOR_6)$NH-heteroaryl, $C(NOR_6)$NH-alkyl-heteroaryl,
$C(NOR_6)$NH-heterocylcoalkyl, $C(NOR_6)$NH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_6 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

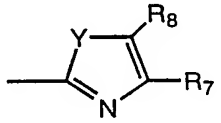
R_7 and R_8 are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, subsituted aryl, cycloalkylalkyl, arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

5. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is NR_9;

R_4 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylalkyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl,

heterocycloalkylalkyl; or

CO-alkyl, CO-cycloalkyl, CO-aryl, CO-alkyl-cycloalkyl, CO-alkyl-aryl, CO-heteroaryl, CO-alkyl-heteroaryl, CO-heterocycloalkyl, CO-alkyl-heterocycloalkyl; or

CONH-alkyl, CONH-cycloalkyl, CONH-aryl, CONH-alkyl-cycloalkyl, CONH-alkyl-aryl, CONH-heteroaryl, CONH-alkyl-heteroaryl, CONH-heterocycloalkyl, CONH-alkyl-heterocycloalkyl; or

COO-alkyl, COO-cycloalkyl, COO-aryl, COO-alkyl-cycloalkyl, COO-alkyl-aryl, COO-heteroaryl, COO-alkyl-heteroaryl, COO-heterocycloalkyl, COO-alkyl-heterocycloalkyl; or

SO_2-alkyl, SO_2-cycloalkyl, SO_2-aryl, SO_2-alkyl-cycloalkyl, SO_2-alkyl-aryl, SO_2-heteroaryl, SO_2-alkyl-heteroaryl, SO_2-heterocycloalkyl, SO_2-alkyl-heterocycloalkyl; or

C(NCN)NH-alkyl, C(NCN)NH-cycloalkyl, C(NCN)NH-aryl, C(NCNNH)-alkyl-cycloalkyl, C(NCN)NH-alkyl-aryl, C(NCN)NH-heteroaryl, C(NCN)NH-alkyl-heteroaryl, C(NCN)NH-heterocycloalkyl, C(NCN)NH-alkyl-heterocylcoalkyl; or

$C(NNO_2)NH$-alkyl, $C(NNO_2)NH$-cycloalkyl, $C(NNO_2)NH$-aryl, $C(NNO_2)NH$-alkyl-cycloalkyl, $C(NNO_2)NH$-alkyl-aryl, $C(NNO_2)NH$-heteroaryl, $C(NNO_2)NH$-alkyl-heteroaryl, $C(NNO_2)NH$-heterocyloalkyl, $C(NNO_2)NH$-alkyl-heterocycloalkyl; or

C(NH)NH-alkyl, C(NH)NH-cycloalkyl, C(NH)NH-aryl, C(NH)NH-alkyl-cycloalkyl, C(NH)NH-alkyl-aryl, C(NH)NH-heteroaryl, C(NH)NH-alkyl-heteroaryl, C(NH)NH-heterocycloalkyl, C(NH)NH-alkyl-heterocycloalkyl; or

C(NH)NHCO-alkyl, C(NH)NHCO-cycloalkyl, C(NH)NHCO-aryl, C(NH)NHCO-alkyl-cycloalkyl, C(NH)NHCO-alkyl-aryl, C(NH)NHCO-heteroaryl, C(NH)NHCO-alkyl-heteroaryl, C(NH)NHCO-heterocylcloalkyl, C(NH)NHCO-alkyl-heterocycloalkyl; or

$C(NOR_6)NH$-alkyl, $C(NOR_6)NH$-cycloalkyl, $C(NOR_6)NH$-aryl, $C(NOR_6)NH$-alkyl-cycloalkyl, $C(NOR_6)NH$-alkyl-aryl, $C(NOR_6)NH$-heteroaryl, $C(NOR_6)NH$-alkyl-heteroaryl, $C(NOR_6)NH$-heterocylcoalkyl, $C(NOR_6)NH$-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_6 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R_7 and R_8 are independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, subsituted aryl, cycloalkylalkyl, arylalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

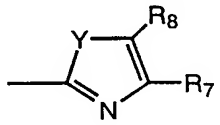
R_9 is hydrogen, alkyl, cycloalkyl, aryl, cycloalkylakyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

m is an integer of 0 to 2; and

n is an integer of 1 to 3.

6. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is oxygen;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-cycloalkyl, CO-alkyl-heteroaryl, CO-alkyl-heteroalkyl, CO-alkyl-heterocycloalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen; and

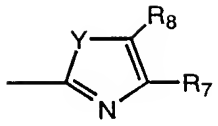
R_7 and R_8 are hydrogen;

m is the integer 0; and

n is the integer 1.

7. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is oxygen;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

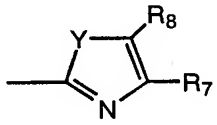
R_7 and R_8 are alkyl;

m is the integer 0; and

n is the integer 1.

8. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is oxygen;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_7 is hydrogen;

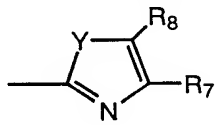
R_8 is alkyl;

m is the integer 0; and

n is the integer 1.

9. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is oxygen;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_7 is alkyl;

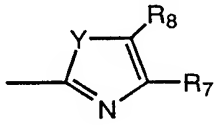
R_8 is hydrogen;

m is the integer 0; and

n is the integer 1.

10. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is sulfur;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_7 is hydrogen;

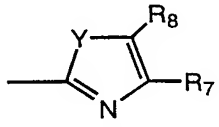
R_8 is alkyl;

m is the integer 0; and

n is the integer 1

11. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is sulfur;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_7 is alkyl;

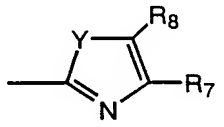
R_8 is hydrogen;

m is the integer 0; and

n is the integer 1.

12. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is NR_9;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_7 is hydrogen;

R_8 is alkyl;

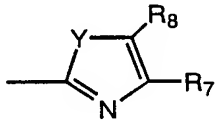
R_9 is hydrogen, alkyl, cycloalkyl, aryl, alkyl-cycloalkyl, alkyl-aryl, heteroaryl, alkyl-heteroaryl, heterocycloalkyl, or alkyl-heterocycloalkyl;

m is the integer 0; and

n is the integer 1.

13. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein Y is NR_9;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-alkyl-heteroalkyl, CO-cycloalkyl, CO-alkyl-heterocycloalkyl, CO-alkyl-heteroaryl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_7 is alkyl;

R_8 is hydrogen;

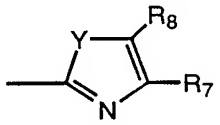
R_9 is alkyl;

m is the integer 0; and

n is the integer 1.

14. The compounds as recited in Claim 1, wherein

R_1 and R_2 are independently hydrogen, fluorine or alkyl;

R_3 is 

wherein X is NR_9;

R_4 is CO-alkyl, CO-alkyl-aryl, CO-cycloalkyl, CO-alkyl-heteroaryl, CO-alkyl-heteroalkyl, CO-alkyl-heterocycloalkyl, CONH-alkyl, CONH-alkyl-aryl, CONH-cycloalkyl, or CONH-alkyl-heterocycloalkyl;

R_5 is hydrogen;

R_7 is alkyl;

R_8 is hydrogen;

R_9 is hydrogen;

m is the integer 0

n is the integer 1.

15. The compound as recited in Claim 1, which is

N-[5-[[5-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide;

N-[5-[[5-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]benzamide;

N-[5-[[5-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl] benzenesulfonamide;

N-[5-[[(4,5-Dimethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide;

N-[5-[[(5-t-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide;

N-[5-[[5-t-Butyl-2-oxazolyl)methyl]thio]-2-thiazolyl]trimethylacetamide;

N-[5-[[(4-Ethyl-2-oxazolyl)methyl]thio]-2-thiazolyl]acetamide; or

a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition comprising a compound of Claim 1, in combination with a pharmaceutically acceptable carrier, and an anti-cancer agent formulated as a fixed dose.

18. A pharmaceutical composition according to claim 16, comprising a compound of Claim 1 in combination with a pharmaceutically acceptable carrier, with an anticancer treatment or anticancer agent administered in sequence.

19. The pharmaceutical composition according to Claim 18, wherein said combination comprising said compound of Claim 1 and said pharmaceutically acceptable carrier, is administered prior to administration of said anticancer treatment or anticancer agent.

20. The pharmaceutical composition according to claim 18, wherein said combination comprising said compound of Claim 1 and said pharmaceutically acceptable carrier, is administered after administration of said anticancer treatment or anticancer agent.

21. A method of inhibiting protein kinases which comprises administering to a mammalian specie in need thereof an effective protein kinase inhibiting amount of a compound of Claim 1.

22. A method of inhibiting cyclin dependent kinases which comprises administering to a mammalian specie in need thereof an effective cyclin dependent kinase inhibiting amount of a compound of Claim 1.

23. A method of inhibiting cdc2 (cdk1) which comprises administering to a mammalian specie in need thereof an effective cdc2 inhibiting amount of a compound of Claim 1.

24. A method of inhibiting cdk2 which comprises administering to a mammalian specie in need thereof an effective cdk2 inhibiting amount of a compound of Claim 1.

25. A method of inhibiting cdk3 which comprises administering to a mammalian specie in need thereof an effective cdk3 inhibiting amount of a compound of Claim 1.

26. A method of inhibiting cdk4 which comprises administering to a mammalian specie in need thereof an effective cdk4 inhibiting amount of a compound of Claim 1.

27. A method of inhibiting cdk5 which comprises administering to a mammalian specie in need thereof an effective cdk5 inhibiting amount of a compound of Claim 1.

28. A method of inhibiting cdk6 which comprises administering to a mammalian specie in need thereof an effective cdk6 inhibiting amount of a compound of Claim 1.

29. A method of inhibiting cdk7 which comprises administering to a mammalian specie in need thereof an effective cdk7 inhibiting amount of a compound of Claim 1.

30. A method of inhibiting cdk8 which comprises administering to a mammalian specie in need thereof an effective cdk8 inhibiting amount of a compound of Claim 1.

31. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

32. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

33. A method for treating inflammation, inflamatory bowel disease, or transplantation rejection, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

34. A method for treating arthritis comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

35. A method for treating infection by HIV, or for treating and preventing the development of AIDS, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

36. A method for treating viral infections, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

37. A method for treating fungal infections, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

38. A method for preventing the development of cancer or tumor relapse, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

39. A method for treating neurodegenerative disease, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 16.

40. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 17.

41. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 17.

42.. A method for preventing the development of cancer or tumor relapse, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 17.

43. A method for treating proliferative diseases comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 18.

44. A method for treating cancer comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 18.

45. A method for preventing the development of cancer or tumor relapse, comprising administering to a mammalian specie in need thereof a therapeutically effective amount of a composition of Claim 18.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/23197

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :C07D 277/54, 417/12; A61K 31/425
US CL :548/181, 184, 185; 514/369
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/181, 184, 185; 514/369

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,254,260 A (TAKAYA et al) 03 March 1981, col. 33, line 58.	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 14 JANUARY 1999	Date of mailing of the international search report 03 FEB 1999
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